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ORIGINAL ARTICLES

ON THE NORMAL URINE SUGAR CURVE IN NORMAL INDIVIDUALS, BORDERLINE DIABETICS AND SEVERE DIABETICS UNDER INSULIN TREATMENT*

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INCIPIENT diabetes may be controlled by such simple therapeusis as diet, therefore its early recognition is of paramount importance.

The following investigation was undertaken with a view to determine a method of recognizing this condition that would involve few technical difficulties, one that was delicate enough to detect small fluctuations in the ability of the individual to prevent sugar wastage, and one that would indicate the state of sugar metabolism for continuous and prolonged periods of time—not momentary states as pictured by blood sugar methods.

The Benedict-Osterberg normal urine sugar method[1] offered such a means, being delicate enough to detect the normal fluctuations in urine sugar and yet flexible enough to determine pathological sugar excretion. Believing that in incipient and borderline cases of diabetes a pathological sugar wastage might occur only at certain intervals—possibly of extraordinarily short duration—we have adopted the plan of analyzing specimens taken at hourly intervals from 7:00 A.M. to 7:00 P.M. and the combined 12 hour specimen of the night. We believe our results justify what might seem to be an excessive number of determinations. The question of diet, nervous influences and other factors will be considered in due order. The investigation covers the 24 hour sugar curves of (1) the normal; (2) borderline diabetics; (3) diabetics on insulin treatment; (4) one case of renal diabetes; (5) one case of borderline diabetes on insulin treatment, and (6) hyperthyroid cases.

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METHODS

The patient is given 13 one hundred c.c. bottles containing a few c.c. of toluene, a 250 c.c. graduate and a list of the foods to be eaten on the test day. Instructions are given to empty the bladder at 7:00 A.M., to collect and measure the urine hourly to 7:00 P.M., saving a sample for analysis. The combined 12 hour night specimen is also saved. All specimens must be kept on ice. The patients must be cautioned that the time of voiding, amount, etc., must be conscientiously recorded. These samples are then taken immediately to the laboratory for analysis. No difficulty will be encountered in getting the patients to void hourly. The test should be started not later than 8:00 A.M. The holding of urine in the bladder prior to the test may cause confusing results due to the diuretic effect of the increased number of voidings.

The specimens were analyzed by the Benedict-Osterberg method, a method which we have found extremely simple and subject to very slight error in the hands of even relatively inexperienced operators.

With regard to this method, our experience has been that certain difficulties may be had in the preparation of suitable bone black. Bone black which liberates a great deal of H_2S and free S on treatment with HCl is very difficult to handle and does not effectively remove interfering substances.

Urine containing albumin causes precipitation on the addition of the picric acid, the precipitate redissolving on the addition of NaOH. We have found only slight variations in the sugar reading when the proteins were previously precipitated with phosphotungstic acid.

Benedict-Osterberg & Neuwirth[2] have shown that the quantity of sugar excreted is independent of volume. Our results amply confirm this view. We have used throughout our work the total sugar excreted in grams (volume × per cent). Per cent seems to have very little significance.

The question of diet is an important one, though less so we must admit than we had believed at the beginning of the work. Two possibilities at least present themselves: (1) that we prescribe a standard diet for all; (2) that we allow the patient to eat the foods to which he is accustomed not only as to quality but also quantity.

So long as the diet is not excessive one way or the other the normal individual keeps well below the line of pathological wastage. Hence variations in diet are of little import. With the borderline diabetic this is a different matter.

In his case there are well defined peaks in the hourly sugar curve after food ingestion, the height of the peaks depending on the quality and quantity of food consumed. The following standard diet has been planned not to limit the patient, but to provide a good ration, quite suitable for the average adult doing a good day's work. In most borderline cases it is high in order that we may determine approximately what the patient can tolerate.

On the other hand certainly a great deal of information is obtained by allowing the patient to follow his own ideas as to diet. Probably for diagnostic purposes the unrestrained diet is the more desirable, but for compara-

tive purposes we have adopted the Standard Diet where it could be feasibly employed.

In the severe diabetics we have tried to employ a diet on which the patient was so-called "sugar free" to the ordinary Fehling and Benedict tests. We have indicated in each curve the exact diet, hence comparisons may readily be made.

STANDARD DIET

BREAKFAST	C	P	F
G. Fruit	5.0	2.0	0.9
Sh. Wheat	23.6	3.1	0 4
Cream	4.6	2.6	19.0
Toast	40.4	6.8	1.2
Sugar	7.0		
Butter			16.2
	81	13	37

DINNER		C	P	F
Butter				16.2
Salad	Orange	10.0		
	Apple	7.1	0.4	0.2
	Celery	1.5	0.6	0.4
Caulif. or 5% Vegetable		1.5	0.6	0.4
Baked apple		14.2	0.8	0.4
Bread		20.2	3.4	0.6
Milk		5.0	3.3	4.0
		70	9	22

SUPPER	C	P	F
Veg. soup	6.0	2.0	0.9
Potato	20.8	2.4	0.1
Milk	5.0	3.3	4.0
Steak		21.9	20.4
Ice cream 50 gms.	36.2	10.6	47.3
Butter			8.1
	68	40	81

Total C. = 219. P. = 62. F. = 140.
Total glucose according to Woodyatt's method of estimation=269.

NORMAL SUGAR EXCRETION

In order to evaluate pathological sugar curves, we must obviously understand the normal. Our first work was carried out with the intention of determining a standard curve of sugar excretion. Four subjects were selected, all in excellent health and performing the same type of work. Specimens were voided at 7:00 A.M., 12:00 M., 5:30 P.M. and 10:30 P.M. The following table gives the results of 216 analyses.

TABLE I

STATISTICAL TABLE OF NORMAL URINE SUGARS

SUBJECT	AVERAGE TOTAL SUGAR 7:00 A. M.	12. M.	5:30 P. M.	10:30 P. M.	TOTAL
P	.252	.189	.207	.221	.869
R	.328	.233	.293	.339	1.193
SW	.339	.218	.377	.388	1.322
Sh	.339	.234	.237	.240	1.050
Average hourly	.039	.043	.050	.054	

The period from 10:30 P.M. to 7:00 A.M. exhibits the lowest level of excretion. From 7:00 A.M. the level of excretion slowly rises. It must be

TABLE II

HOURLY URINE SUGAR IN NORMAL INDIVIDUALS

SUBJECT	TIME	VOLUME	TOTAL SUGAR IN GRAMS	DIET
No. 1. A.J.S.	12 hr.	425	.857	Stand.
	8 A. M.	55	.047	
	9 "	36	.039	
	10 "	52	.048	
	11 "	41	.037	
	12 M.	55	.031	
	1 P. M.	90	.051	
	2 "	100	.080	
	3 "	40	.040	
	4 "	32	.029	
	5 "	26	.024	
	6 "	60	.043	
	7 "	40	.040	
No. 2. E.B.	7 A. M.	53	.031	Stand.
	8 "	20	.020	
	9 "	45	.047	
	10 "	70	.052	
	11 "	83	.034	
	12 M.	57	.023	
	1 P. M.	30	.033	
	2 "	62	.056	
	3 "	55	.039	
	4 "	70	.049	
	5 "	62	0.47	
	6 "	47	.025	
	12 hr.	717	.372	
E.B.	7 A. M.	50	.047	Stand.
	8 "	45	.052	
	9:10 "	85	.063	
	10:15 "	265	.073	
	11 "	90	.028	
	12 M.	145	.062	
	1 P. M.	65	.041	
	2 "	75	.058	
	3:20 "	110	.076	
	4 "	65	.039	
	5 "	120	.077	
	6 "	55	.045	
	12 hr.	1100	.479	
E.B.	7 A. M.	53	.032	Stand.
	8 "	65	.046	
	9 "	90	.044	
	10 "	65	.033	
	11 "	70	.039	
	12 M.	45	.031	
	1 P. M.	120	.067	
	2 "	70	.036	
	3 "	68	.043	
	4 "	50	.033	
	5 "	52	.033	
	6 "	30	.024	
	12 hr.	1110	.555	

SUBJECT	TIME	VOLUME	TOTAL SUGAR IN GRAMS	DIET
No. 3. E.S.	12 hr.	1000	.450	Stand.
	8 A. M.	36	.018	
	9 "	27	.011	
	10 "	23	.009	
	11 "	31	.012	
	12 M.	28	.007	
	1 "	21	.015	
	2 "	15	.009	
	3 "	33	.026	
	4 "	24	.016	
	5 "	31	.019	
	6 "	21	.009	
	7 "	20	.009	
No. 4. I.H.P.	8 hr.	325	.325	Mixed
	8 A. M.	50	.034	
	8:45 "	50	.025	
	10 "	165	.082	
	11 "	65	.055	
	12 M.	205	.059	
	1:30 P. M.	150	.046	
	2:30 "	245	.076	
	3:30 "	50	.030	
	4:30 "	56	.042	
	5:20 "	54	.036	
	6:20 "	150	.040	
	7:20 "	115	.040	
	8:20 "	90	.044	
	9:20 "	40	.047	
	10:20 "	50	.058	
	5 A. M.	240	.218	
	7:20 "	100	.075	
I.H.P.	8:20 A. M.	90	.029	Mixed
	9:20 "	340	.034	
	10:20 "	210	.067	
	11:20 "	195	.019	
	1:20 "	200	.020	
	12:10 P. M.	155	.054	
	2:20 "	75	.054	
	3:20 "	95	.059	
	4:20 "	115	.028	
	5:20 "	230	.049	
	6:50 "	140	.035	
	8:00 "	60	.023	
	9 "	95	.038	
	10 "	35	.040	
	6:00 A. M.	285	.185	
	8 "	190	.039	
No. 5. Reid	8 A. M.	35	.026	Stand.
	9 "	232	.058	
	10 "	80	.040	
	12 M.	45	.031	
	1 P. M.	18	.028	
	11 "	48	.021	
	2 "	140	.068	
	3 "	98	.064	
	4 "	36	.027	
	5 "	42	.036	
	6 "	34	.027	
	7 "	32	.021	
	12 hr.	600	.366	

SUBJECT	TIME	VOLUME	TOTAL SUGAR IN GRAMS	DIET	SUBJECT	TIME	VOLUME	TOTAL SUGAR IN GRAMS	DIET
No. 6. C.H.	12 hr.	720	.248	Stand.	No. 8. R.	12 hr.	260	.153	Stand.
	8 A. M.	70	.043			8 A. M.	36	.018	
	9:20 "	38	.023			9 "	26	.019	
	10:10 "	90	.032			10 "	47	.030	
	11:15 "	170	.059			11 "	70	.029	
	12 M.	50	.016			12 M.	31	.017	
	1 P. M.	50	.027			1 P. M.	36	.018	
	2:15 "	160	.062			2 "	..	....	
	3 "	58	.037			3 "	63	.063	
	4 "	260	.078			4 "	25	.018	
	5 "	240	.072			5 "	39	.024	
	7:15 "	110	.040			6 "	40	.021	
	8:30 "	85	.041			7 "	32	.020	
No. 7. J.M.	8 A. M.	35	.020		No. 9. J.W.	9 A. M.	50	.040	Mixed
	9 "	30	.030			10 "	50	.040	
	10 "	53	.039			11 "	45	.038	
	11 "	115	.049			12 M.	35	.026	
	12 M.	43	.023			1 P. M.	70	.042	
	1:15 P. M.	47	.033			2 "	45	.041	
	2:30 "	35	.044			3 "	30	.033	
	3:30 "	30	.039			4 "	35	.049	
	4:30 "	40	.033			5 "	30	.039	
	5:15 "	22	.016			6 "	35	.033	
	6:15 "	55	.030			7 "	65	.033	
	7 "	38	.023			8 "	100	.058	
	12 hr.	890	.400						

remembered that this type of curve eliminates the hills and valleys, hence is not a true picture of the hourly excretion. The striking thing, however, is the remarkable constancy of sugar excretion.

A number of subjects were now selected as "normals" to be run on the basis of the standard diet and hourly specimens. Table II and Figs. 1 and 2 will give an example of the results. None of these subjects had a history of diabetes nor had sugar even been found in their urines. We may say that in a number of cases supposedly normal, the curve of sugar excretion was not normal according to our conception. These subjects on closer examination showed a borderline diabetes.

The results seem to indicate that in the truly normal individual the sugar curve does not at any time make an excursion above the 90 to 110 mg. level. Points above this level are regarded with suspicion unless subsequently shown to be due to some untoward cause, such, for example, as excessive nervousness, strain, etc. A comparison of the normal with the borderline diabetic curve, however, leaves little doubt as to the nature of the case.

A consideration of the curves will indicate the difficulty of generalizing. We may say that one hour after meals a distinct rise occurs followed by a fall to approximately the original level or below.

The quantity of food ingested does not appear to control this rise to any great extent. In fact the greatest rise appears to come after breakfast and not after supper as illustrated by the record of Mr. I. H. P.

The normal curve varies a great deal from individual to individual but

the one thing in common is that excursions of the curve above the 90 to 110 mg. level do not appear to occur. The cases of Mr. R. (Fig. 2, Table I) and Mr. S. (Table II) illustrate the low levels of normal sugar. Fig. 1 shows that in three successive days on the same diet the excretion from hour to hour is practically identical. However, other subjects apparently just as normal show wide variations from day to day; indeed the same individual (Mr. R.) showed considerable variation after a few days.

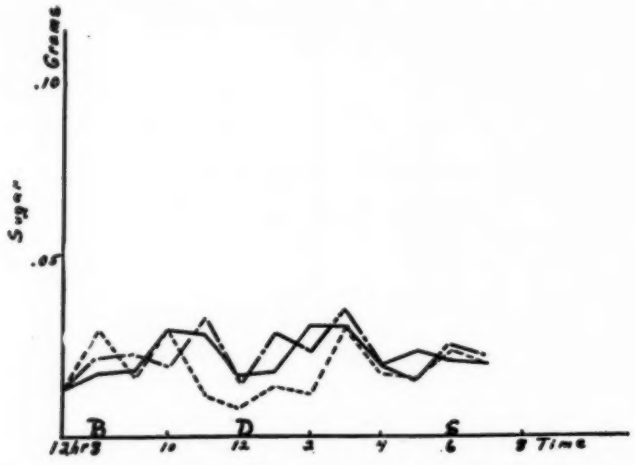

Fig. 1.—Normal hourly sugar curve (Mr. R.) on three successive days. *B*, breakfast; *D*, dinner; *S*, supper. Standard diet.

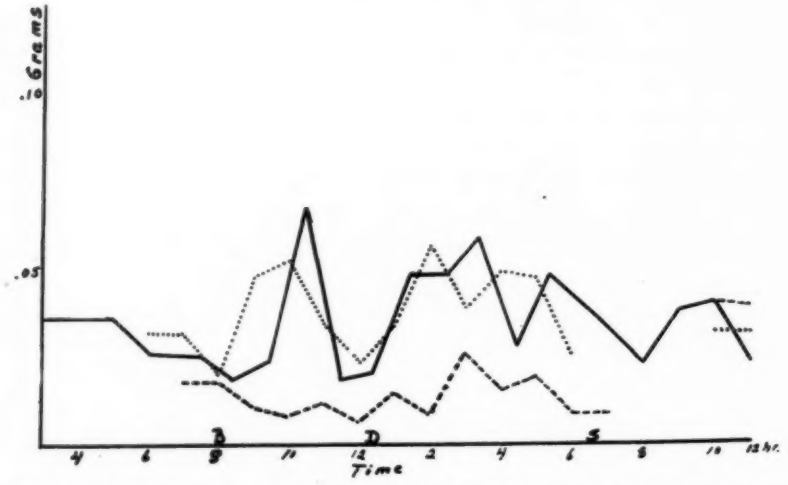

Fig. 2.—Hourly sugar curve of three normal individuals (Mr. B., Mr. S., and Mr. P.). *B*, breakfast; *D*, dinner; *S*, supper. Standard diet.

A great many factors must play a part in the excretion of "normal sugar"—for our purposes, however, we need only consider the causes which produce apparent anomalies in the curve. Certainly the most potent cause is defective sugar metabolism.

Our results would then seem to show (1), considered on a statistical basis, the curve of normal sugar excretion is remarkably constant but with

a slight upward trend from morning to evening, with a low level during sleep; (2), considered on the basis of hourly samples, the quantity of sugar excreted rises for one hour after meals, then sharply falls (the original on a lower level). The rise is in no way dependent upon the quantity or quality of food ingested. In general the greatest rise appears to follow breakfast; (3), the curve of our so-called normal cases does not exhibit excursions above the 90 to 110 mg. level; (4), great variations and remarkable constancies of sugar excretion may occur at different times in the same individual.

In all cases breakfast was eaten at approximately 7:15 to 7:30, dinner at 12 to 12:30 and supper 6:00 to 6:45.

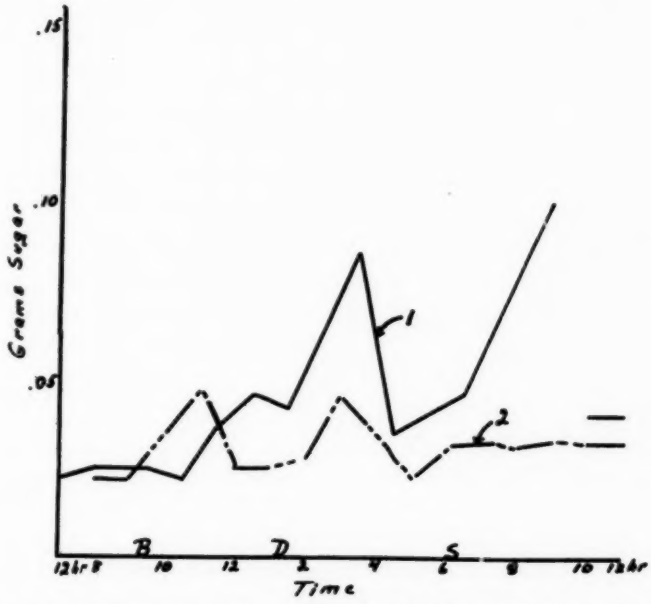

Fig. 3.—Hourly sugar curve of Mr. S., a very mild diabetic. Curve 1, test run on Sunday with no exercise—patient slightly nervous. Curve 2, taking exercise out of doors.

BORDERLINE AND SUSPECTED DIABETICS

The remarkable thing about this class of patients is their apparent ability to maintain a sugar-free urine except 2 to 4 hours a day. These so-called "breaks" generally occur 1½ hours or longer after meals and may last one to two hours. Following such a break a precipitous fall supervenes which may last three to four hours, again followed by another break. We have considered any excursion above the 90 to 110 mg. level as a "break." However, as Figs. 3 and 4, Tables III and IV, will show, one is seldom in doubt as to whether or not a break has occurred.

CASE RECORDS

CASE 10, T. S.:—Sugar first noticed in August of 1921. The sugar was not detected until the third examination. The week before the test he had been under excessive nervous strain in court. Weight fluctuations have been very marked. Since the appearance of sugar he has lost 16 lbs, but appears to be fairly stable at the date of the tests.

TABLE OF HISTORIES III

SUBJECT	SEX	AGE	HEIGHT	WEIGHT POUNDS	VASCULAR CONDITION	KIDNEYS	OCCUPATION
No. 10. T. S.	Male	36	6'	184	Good	Good	Lawyer
No. 11. H. E.	Female	52	5' 5"	139	Good	Good	Head bookkeeper
No. 12. E. B.	Female	77	5' 6"	140	Fair	Alb.	Housewife
No. 13. H.	Male	29	5' 9"	125	Vascular trouble	Good	Machinist
No. 14. J.	Male	26	6' ½"	131	Palpitation	Good	Telegraph operator
No. 15. McN.	Male	58	5' 10"	167	Good	Good	Manufacturer
No. 16. Rev. W.	Male	43			Slight sclerosis	Good	Minister
No. 17. Dr. B.	Male	36	5' 9¾"	204	Good	Good	Doctor
No. 18. So.	Male	38	5' 8½"	152	Good	Good	Doctor
No. 19. Co.	Male	70	4' 5"	133	Sclerotic	Fair	Retired merchant

Fig. 3. Curve 1. 4/15/23 Breakfast C=62, P=44, F=42, Lunch C=2, P=13, F=25, Supper C=30, P=31, F=33. Total C=94, P=88, F=110. T. G.=156.

The test was made on Sunday, following a three day trip. T. S. sometimes showed sugar after such a trip but found no sugar on Saturday night. He did not take his accustomed exercise on Sunday and became slightly nervous toward evening.

Curve 2. 4/22/23 Breakfast C=81, P=13, F=37, Lunch C=70, P=9, F=22, Supper C=68, P=40, F=81, Total C=219, P=62, F=150, T. G.=270. Test made on Sunday. Patient worked on his car all day out of doors and felt in excellent condition.

Table IV. 5/2/23 Breakfast C=121, P=37, F=65, Lunch C=100, P=29, F=61, Supper C=58, P=45, F=56, Total C=279, P=111, F=182, T. G.=361.

The test was made during an average day's work at his office. No special worry was involved.

It is interesting in this case to note that T. S. exhibited a break on the day on which the total glucose content of the meals was least (T. G.=156). While doing his regular day's work at the office even though the glucose content of the diet was three times that of the diet on which he "broke" the curve appears quite normal.

CASE 11, H. E.:—Sugar first noticed October 1922. No sugar found 3 years before when a tonsillectomy was performed. Patient was losing weight rapidly up to November, 1922, when she was put to bed for a general rest to clear her of sugar. During 1921-1922 she had noticed some signs of polyphagia, and polyuria. She had been under excessive mental strain shortly before sugar was found. Her mother and father both had diabetes, but none has been found in her brother so far as she knew. The patient was able to do a normal days work and apparently enjoyed reasonably good health.

Fig. 4. Curve 1. 4/22/23. The Standard Diet was used, the test was made on Sunday, thus giving the patient an easy, restful day. This diet is not above that to which the patient was accustomed.

Table IV. B. 5/3/23. The Standard Diet was again followed but the test was run during regular office hours. Consideration of these curves leaves little doubt as to the existence of disordered sugar metabolism. Surely it is such cases as these that we must stop from their downhill progress.

CASE 12, E. B.:—Sugar was first noted 20 years before test. At the time none of the cardinal symptoms of diabetes were exhibited. She continued to show small amounts of sugar until a gangrenous toe of eight years' standing was amputated. About one year after this her leg was accidentally hurt and up to date, three years in all, has not healed. Her weight has been fairly constant and other than the wound on her leg, she appears in excellent health. We, of course, suspected defective sugar metabolism as the cause of the nonhealing of the wound. Aside from a slightly erratic curve we have not been able to detect any diabetes.

Table IV. 4/18/23. Standard Diet. Patient spent a quiet day at home. Some albumin was found.

Table IV. 5/6/23. The test was run on Sunday using the Standard Diet. The day was quiet and uneventful.

CASE 13, Mr. H.:—So far as the patient knew this was the first time sugar had been found. He entered the hospital to be under observation for appendicitis. The only history of diabetes was the death of a great aunt from that disorder.

Table IV. 4/4/23. Breakfast, C=40, P=8, F=30, Lunch, C=60, P=12, F=36, Supper, C=183 P=50, F=116, Total C=283, P=70, F=183, T. G.=342. The case was ambulatory but most of the test day was spent in bed.

CASE 14, Mr. J.:—No sugar had been found previous to this test. The family history was negative so far as diabetes was concerned. He entered the hospital for nervousness. Polyuria was rather marked but only a slight polyphagia.

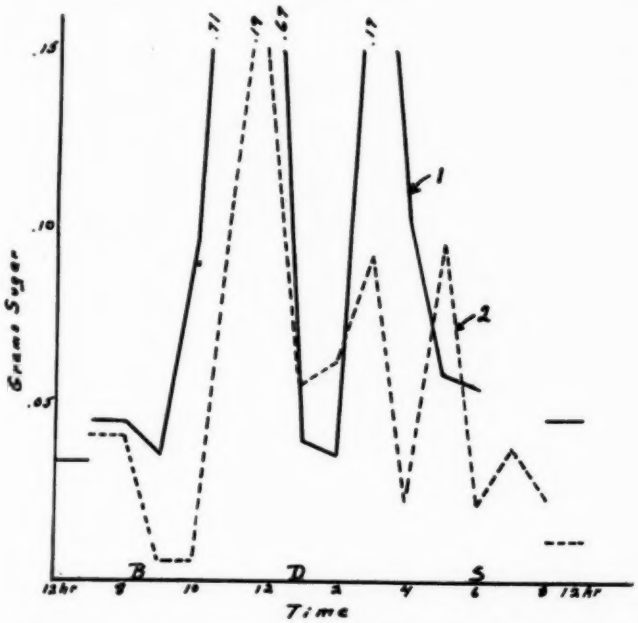

Fig. 4.—Hourly sugar curve of two suspected diabetics on standard diets. Curve 1, Miss E., and Curve 2, Rev. W.

Table IV. 3/4/23. Breakfast, C=63, P=11, F=31, Lunch, C=81, P=13, F=7, Supper, C=81, P=13, F=7, Total C=225, P=47, F=45, T. G.=257.

CASE 15, Mr. McN.:—A slight amount of sugar was first noted six weeks before the test. The family history was negative for diabetes. The patient appeared in excellent physical condition. Fasting blood sugar=.089%.

Table IV. 4/6/23. The Standard Diet was used.

CASE 16.—Rev. W. Sugar first found when the patient was a child. Had been again found three days before our test, in one specimen only (after noon meal), examination showed a badly deflected septum, chronic congestion and poor drainage of the sinuses, irritable colon, nervousness, abdominal discomfort and headaches. Fasting blood sugar =.087% while 11:00 A. M. Blood sugar =.167%.

Fig. 4, 4/9/23. The Standard Diet was used during the test. Total C=219, P=62, F=140, T. G.=269.

CASE 17.—B. Apparently has shown small amounts of sugar intermittently for two years. Basal metabolism=20%.

TABLE IV

BORDERLINE OR SUSPECTED DIABETICS

CASE NO.	TIME	VOLUME	TOTAL SUGAR GRAMS
No. 10. T.S.	5/2/23		
	7 A. M.	1160	.243
	8 "	85	.030
	9 "	144	.049
	10 "	71	045
	11 "	45	.032
	12 M.	75	.048
	1 P M.	75	.060
	2:35 "	100	.048
	3:35 "	75	.034
	4:35 "	60	.040
	5:35 "	54	.030
	6:35 "		.027
	7:35 "		.030
	12 hr.		.307
No. 11. H.E.	5/3/23		
	12 hr.	500	1.06
	8 A. M.	325	.109
	9 "	285	.749
	10 "	125	.832
	11 "	90	.642
	12 M.	70	.205
	1 P. M.	45	.040
	2 "	125	.056
	3 "	110	.456
	4 "	120	.999
	5 "	65	.541
	6 "	180	.257
	12 hr.	800	.896
No. 12. E.B.	4/18/23		
	7 A. M.	57	.030
	8 "	47	.042
	9 "	15	.014
	10 "	40	.034
	11 "	55	.049
	12 M.	50	.042
	1 P. M.	30	.019
	2 "	25	.024
	3 "	47	.049
	4 "	45	.049
	5 "	65	.057
	6 "	67	.046
	12 hr.	1255	.404
No. 12. E.B.	5/6/23		
	8 A. M.	120	.059
	9 "	47	.048
	10 "	15	.015
	11 "	45	.052
	12 M.	55	.036
	1 P. M.	55	.067
	2 "	25	.020
	3 "	30	.029
	4 "	60	.042
	5 "	55	.036
	6 "	87	.050
	7 "	50	.036
	12 hr.	1130	.588

CASE NO.	TIME	VOLUME	TOTAL SUGAR GRAMS
No. 13. H.	4/4/23		
	9 A. M.	60	.052
	10 "	170	.040
	11 "	190	.024
	12 M.	180	.019
	1 P. M.	80	.037
	2 "	380	.148
	3 "	200	.080
	4 "	150	.015
	5 "	280	.291
	6 "	106	.108
	7 "	55	.036
	8 "	90	.168
	9 "	60	.138
	12 hr.	340	.102
No. 14. J.	3/4/23		
	9 A. M.	330	.003
	10 "	no voiding	
	11 "	52	.023
	12 M.	330	.004
	1 P. M.	210	.037
	2 "	380	.034
	3 "	80	.014
	4 "	250	.022
	5 "	80	.025
	6 "	60	.049
	7 "	180	.221
	8 "	450	.265
	9 "	90	.036
	12 hr.	800	.416
No. 15. McN.	4/6/23		
	12 hr.	660	.217
	8 A. M.	200	.128
	9 "	115	.037
	10 "	230	.055
	11 "	200	.182
	12 M.	260	.189
	1 P. M.	65	.046
	2 "	150	.033
	3 "	150	.033
	4 "	80	.030
	5 "	290	.087
	6 "	180	.088
	7 "	60	.010
	8 "	110	.063
	12 hr.	500	.115
No. 17. B.	4/18/23		
	10 A. M.	100	.088
	11 "	38	.030
	12 M.	42	.031
	1 P. M.	25	.021
	2 "	55	.052
	3 "		
	4 "	100	.097
	5 "	90	.066
	6 "	25	.017
	7 "	40	.036
	8 "	50	.050
	12 hr.	450	.351

TABLE IV—CONT'D.

BORDERLINE OR SUSPECTED DIABETICS

CASE NO.	TIME	VOLUME	TOTAL SUGAR GRAMS
No. 17. B.	4/24/23		
	10 A. M.	65	.079
	11 "	65	.057
	12 M.	50	.048
	1 P. M.	30	.029
	2 "	30	.027
	3 "	52	.042
	4 "	60	.048
	5 "	65	.042
	6 "	55	.048
	7 "	38	.043
	12 hr.	475	.365
No. 18. Sp.	2/6/23		
	11 A. M.	160	.209
	12 M.	120	.051
	1 P. M.	125	.042
	2 "	120	.033
	3 "	140	.109
	4 "	80	.066
	5 "	150	.076
	6 "	150	.046
	7 "	160	.009
No. 18. Sp.	5/13/23		
	8 A. M.	45	.036
	9 "	40	.055
	10 "	25	.028
	11 "	30	.035
	12 M.	30	.033
	1 P. M.	23	.031
	2 "	48	.060
	3 "	50	.051
	4 "	50	.054
	5 "	35	.032
	6 "	35	.045
	7 "	75	.089
	12 hr.	890	.795
No. 18. Sp.	4/15/23		
	8 A. M.	25	.020
	9 "	35	.059
	10 "	35	.049
	11 "	30	.037
	12 M.	25	.031
	1 P. M.	25	.035
	2 "	35	.159
	3 "	35	.117
	4 "	20	.034
	5 "	40	.056
	6 "	25	.031
	7 "	30	.060
	8 "	55	.093
	9 "	45	.037
	10 "	120	.085
	7 A. M.	890	.400
No. 19. Co.	9 A. M.	25	.025
	10 "	200	.066
	11 "	350	.129
	12 M.	210	.065
	1 P. M.	180	.075
	2 "	300	.117
	3 "	100	.041
	4 "	150	.064
	5 "	100	.041
	6 "	150	.060
	7 "	75	.080
	12 hr.	525	.676

Table IV. 4/18/23 and 4/24/23. The Standard Diet was used.

CASE 18. Sp. Sugar first noted in 1921 but disappeared until January, 1923. He had been frequently examined prior to 1921 but the results were negative. Patient does not know of any reason for the first appearance of sugar. At the time of the test No. 9 Sp. had a focal infection in a molar tooth and some infected tonsilar tissue. Fehling's solution tests had been negative and were negative at the time of the test. The results from the glucose tolerance test (85 grams glucose) were as follows:

	Blood Sugar	Urine sugar
Normal	.114	.02 %
1st hour	.142	3.0 %
2nd hour	.135	.8 %
3rd hour	.097	.01 %

Table IV. 2/6/23.

Test taken while patient was resting in the hospital. C=60, P=45, F=145, T. G.=100. 11:00 A. M. Blood sugar, 116%

Table IV. 5/13/23.

Test run on Sunday—some exercise and considerable rest. Standard Diet used.

Table IV. 5/15/23.

Patient operated in the morning and spent a very busy day at his office. The Standard Diet was again used.

CASE 19. Co.—A slight amount of sugar was first detected 1½ years before the test and has intermittently appeared since then. All blood sugars have been normal. The following results were obtained with the glucose tolerance test.

	Blood Sugar	Urine Sugar in grams
Normal	.088	.06
30 min. after glucose	.170	.17
1½ hrs.	.160	.18
3 hrs.	.073	.03

Diacetic and acetone free. Fasting blood sugar .104%.

At the present time the patient had some nitrogen retention (Blood Urea N_2=25 mg. and uric acid 3.7 mg.). Parkinson's disease also was found.

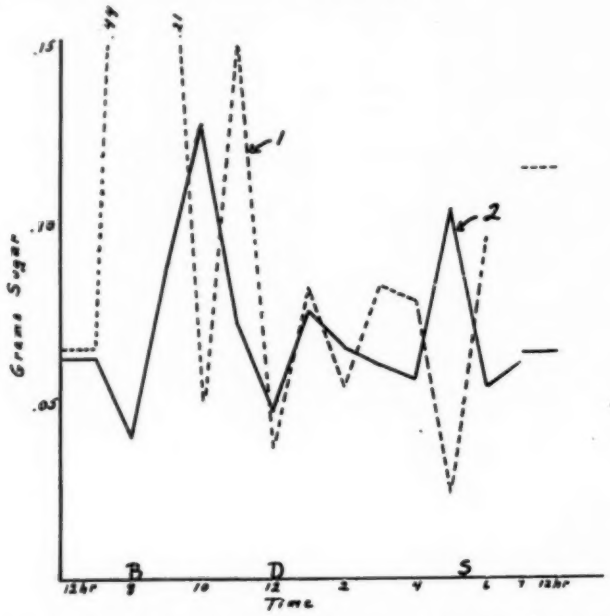

Fig. 5.—Hourly sugar curve of two very severe diabetics under insulin treatment. Curve 1, Mr. S. W., 6 units insulin at 8 a. m., 12 m., and 5 p. m. Curve 2, Mr. Wa., 4 units insulin at 8 a. m., 12 m., and 5 p. m.

BORDERLINE DIABETES UNDER INSULIN TREATMENT

It became of interest to determine what effect insulin would have on the small amounts of sugar intermittently thrown out by borderline diabetics. The following case will illustrate the effect.

CASE 30.—Mr. J. B. Sugar first noticed about 10 months before this test. Patient under treatment for bowel trouble when sugar was found. It appearance since then has been intermittent. No. 30 J. B. is Jewish and of a nervous disposition. His work required considerable mental strain and worry. Glucose tolerance test (85 grams glucose) showed apparently no abnormality whatever in the sugar metabolism.

	Blood Sugar	Total Grams Urine Sugar
Normal Fasting	.83	.04
1st hour	.153	.10
2nd hour	.105	.09
3rd hour	.084	.04

Immediately after the test hourly specimens were voided and the normal urine sugar determined. Table VII 5/10/23 presents the results with the results from the following day on our Standard Diet.

SEVERE DIABETICS UNDER INSULIN TREATMENT

The following group of patients comprise the group known as severe diabetics. In practically all cases the patients had been desugarized by the insulin treatment.

TABLE OF HISTORIES OF DIABETICS UNDER INSULIN TREATMENT (SEE TABLE V)

NO.	SUBJECT	SEX	AGE	WEIGHT LBS.	HEIGHT	VASCULAR	KIDNEYS	OCCUPATION
No. 20	Swa	Male	42	92	5'11"	good	fair	Manager
No. 21	Watj.	Male	28	129	5' 8"	good	good	Coal Miner
No. 22	Wes.	Male	14	72	5' 2"	good	good	School Boy
No. 23	H	Male	17	103	5' 6"	good	Alb.	Student
No. 24	E	Male	24	110	5' 6¾"	good	good	Student
No. 25	Swin.	Male		187	5' 9"	good	Alb.	
No. 26	Crawf.	Male	16			good		School Boy

CASE 20.—Swa. A very severe diabetic of 3 years' standing. Blood sugar at 11 A. M. one day of test=212%. Fig. 5 No. 1. Total C=65, P=40, F=150, T. G.=103. The diet was equally distributed throughout the three meals. Six units of insulin were given 15 minutes before each meal.

CASE 21.—Wa. This is a case of fair severity with onset following an attack of "flu." Fig. 5 No. 2. Total C=70, P=45, F=170, T. G.=113 equally distributed throughout the three meals. Four units of insulin were given 15 minutes before each meal.

Case 22.—Mr. W. Twelve days before the test the patient was in coma, with blood sugar of .666%, on insulin he became sugar-free in six days. Twelve days after his coma the test was run. Blood sugar on test day=100%. Fig. 6 No. 2, 5/3/23. Total C=75, P=35, F=140, T. G.=109 equally distributed throughout 3 meals. Two units insulin at 8 A. M. and 2 units at 5:000 P. M.

CASE 23.—Mr. H. This is a case of severe diabetes sugar-free on insulin. 11:00 A. M. blood sugar equalled .085% on the day of the first test.

Fig. 6 No. 1. Total C=80, P=45, F=185, T. G.=125 equally distributed throughout 3 meals. Five units of insulin were given at 8:00 A. M.

Table V. 4/12/23. Diet as in Fig. 5 No. 1 but 3 units of insulin were given at 8 A. M. and 3 units at 5 P. M.

CASE 24.—Mr. E. A case exhibiting all the cardinal symptoms of severe diabetes of four years' standing. Table V. 3/5/23. Total C=70, P=45, F=160, T. G.=122. Twelve units of insulin given at 8 A. M., twelve units at 12 M. and twelve units at 5 P. M. Table V. 3/6/23. Diet and insulin same as in curve A.

CASE 25.—Mr. Swin. Sugar first noticed in October of 1922. Cardinal symptoms of diabetes mild, but the patient was hard to desugarize. Table V. 3/2/23. Total C=65, P=40, F=160, T. G.=104. The patient had breakfast but no lunch. Blood sugars at 11 A. M.=200%, 12 M.=265% 1 P. M.=235%, 2 P. M.=250%, 3 P. M.=247%, 5 P. M.=220% Thirty units insulin were given by mouth at 11 A. M. with 6 oz. ice water. In this form the insulin is obviously ineffective. Two units insulin were given subcutaneously at 5 P. M. C=65, P=40, F=160 T. G.=104. Three units of insulin given at 8 A. M., 12 M. and 5 P. M. Total C=75, P=50, F=160, T. G.=122. Seven units of insulin were given at 8 A. M., 12 M. and 5 P. M.

TABLE V

SEVERE DIABETICS UNDER INSULIN TREATMENT

CASE NO.	TIME	VOLUME	TOTAL SUGAR GRAMS
No. 23. H.	4/12/23		
	9	20	.020
	10	180	.041
	11	220	.040
	12	120	.037
	1	220	.037
	2	240	.053
	3	160	.034
	4	200	.050
	5	100	.025
	6	100	.022
	7	140	.019
	8	180	.029
No. 24. E.	3/5/23		
	8	44	.070
	9	33	.066
	10	74	.042
	11	119	.310
	12	89	.338
	1	200	.156
	2	130	.117
	3	125	.100
	4	95	.098
	5	100	.054
	6	50	.025
	7	100	.069
	12 hr.	750	.405
No. 24. E.	3/6/23		
	10	220	.352
	11	220	.242
	12	50	.060
	1	230	.078
	2	280	.044
	3	400	.120
	4	240	.054
	5	110	.041
	6	900	.050
	7	280	.058
	12 hr.	600	.240
No. 25. S.	3/2/23		
	11	150	.610
	12	120	.430
	1	65	.180
	2	75	.290
	3	50	.110
	4	50	.120
	5	25	.040
	6	30	.060
	7	230	.250
	12 hr.	280	1.000
No. 25. S.	3/8/23		
	12 hr.	600	1.134
	8	150	.299
	9	120	.114
	10	180	.581
	11	500	1.49
	12	200	.624
	1	280	.414
	2	240	.480
	3	320	.800
	4	150	.468
	5	100	.143
	6	120	.277
No. 25. S.	3/30/23		
	12 hr.	700	.424
	7	100	.050
	8	100	.046
	9		
	10	500	.125
	11	260	.084
	12	400	.064
	1	260	.006
	2	320	.114
	3	120	.055
	4	100	.047
	5	120	.064
	6	80	.038

GLUCOSE TOLERANCE TEST

	BLOOD SUGAR	TOTAL URINE SUGAR GRAMS
Normal	.080%	.070
1st hour after glucose	.172%	.056
2nd hour	.143%	.090
3rd hour	.090%	.041
4th hour	.082%	.022
5th hour	.078%	.022

RENAL DIABETES

CASE 26.—Cr. First showed sugar at two years of age and has maintained a persistent glycosuria with a constantly normal blood sugar. The glucose tolerance test was not abnormal.

This case has shown some acetone and acetoacetic acid thus pointing to some complicating pancreatic diabetes. The insulin treatment seems to have a certain amount of value in this case.

Table VI. 4/18/23. Total C=65, P=40, F=165, T. G.=104. Samples were taken at two hourly intervals—for comparison with the other data, they must be calculated to an hourly

basis. This curve has been repeated twice on the same diet with results that are practically identical. Table VI. 5/1/23. Total C=85, P=50, F=190, T. G.=128. These units of insulin at 8 A. M. and 5 P. M. were given. Samples in this case were collected hourly. Table VI. 2/26/23. Total C=65, P=40, F=165, T. G.=104.

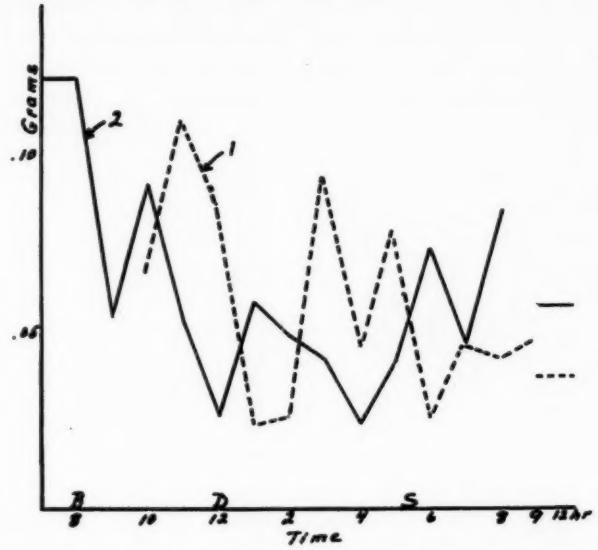

Fig. 6.—Hourly sugar curve of two diabetics undergoing insulin treatment. Curve 1, Mr. H., 5 units insulin at 8 a. m. Curve 2, Mr. W., 2 units insulin at 8 a. m., and 5 p. m.

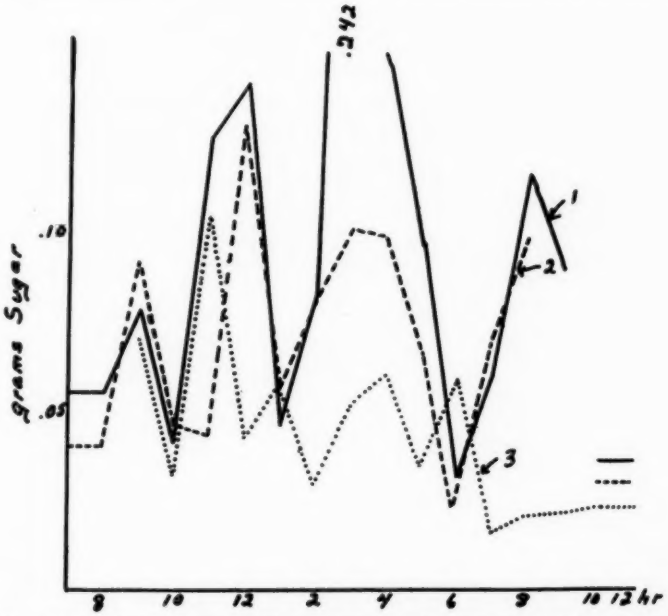

Fig. 7.—Mr. J. B. Borderline diabetes under insulin treatment. Curve 1, control day on standard diet. Curve 2, standard diet with three units of insulin at 10 a. m., and 5:30 p. m. Curve 3, standard diet with two units of insulin at 8:30 a. m., 12 m., and 5:30 p. m. Meals were served at 8 a. m., 12:30 p. m., and 5:45 p. m.

It is very striking that shortly after a so-called "normal" glucose tolerance test the patient exhibited three excessive "breaks." A week after this test No. 30, J. B., again returned to the hospital. Fig. 7, Curve No. 1, pre-

sents the first control day. Curve No. 2 presents the following day with 3 units insulin at 10 A.M. and 3 units at 6 P.M. Curve No. 3 presents the results of the next day with 2 units insulin at 8:30 A.M. and 2 units at 12 M., and 2 units at 5:30 P.M. The Standard Diet was used throughout.

It is a question for the future to decide whether insulin treatment would be an aid in preventing the downhill progress of such a mild glycosuria. Certainly it is a question of the utmost importance.

TABLE VI.

RENAL GLYCOSURIA

CASE NO.	TIME	VOLUME	TOTAL SUGAR GRAMS	CASE NO.	TIME	VOLUME	TOTAL SUGAR GRAMS
No. 26. Cr.	4/18/23			No. 26. Cr.	5/1/23		
	9 A. M.	50	.185		7 A. M.	50	.217
	11 "	60	.190		8 "	60	.124
	1 P. M.	80	.260		9 "	60	.499
	3 "	80	.500		10 "	60	.461
	5 "	60	.190		11 "	40	.114
	7 "	80	.260		12:30 P. M.	80	.190
	12 hr.	900	1.278		2 "	80	.420
No. 26. Cr.	2/26/23				3 "	95	.286
	10 A. M.	60	1.2		4 "	60	.153
	12 M.	200	1.0		6 "	80	.144
	2 P. M.	220	2.4		12 hr.	950	1.43
	4 "	250	1.6				
	6 "	300	2.7				
	8 "	85	.7				
	12 hr.	460	3.5				

TABLE VII

BORDERLINE DIABETIC AFTER TOLERANCE TEST

5/10/23	TIME	VOLUME	TOTAL SUGAR GRAMS	5/11/23	TIME	VOLUME	TOTAL SUGAR GRAMS
	9:50 A. M.	220	.098		9 hr.	610	.287
	10:50 "	150	.063		8 A. M.	30	.016
	11:50 "	325	.100		9 "	160	.064
	12:50 P. M.	425	.129		10 "	290	.088
	1:50 "	120	.050		11 "	245	.067
	2:50 "	200	.086		12 M.	425	.106
	3:50 "	400	.129		1 P. M.	250	.085
	4:50 "	425	.139		2 "	175	.068
	5:50 "	90	.038		3 "	75	.055
	6:50 "	100	.052		4 "	215	.086
	7:50 "	360	.450		5 "	150	.065
	8:50 "	120	.117		6 "	345	.143
					7 "	220	.101
					9 hr.	765	.382

Our experience with dogs has been that very considerably more insulin is required to bring the urine sugar below the "normal" level than is required to bring the excess sugar in a hyperglycemia down to this normal level. The diabetic is infinitely more sensitive to insulin than the normal individual.

HYPERTHYROID CASES

CASE 27.—Mr. Blen. Age sixty-nine, height 5′ 8″, weight 110 lbs. This case has had a colloid goiter for 30 to 35 years. Sugar was found in the urine about two months before this

TABLE VIII

HYPERTHYROID CASES

CASE NO.	TIME	VOLUME	TOTAL SUGAR GRAMS	CASE NO.	TIME	VOLUME	TOTAL SUGAR GRAMS
No. 27. Blair	12 hr.	1000	.062	No. 29 C. M	9 A. M.	50	.038
	9 A. M.	100	.057		11 "	80	.060
	10 "	30	.021		1 P. M.	120	.126
	11 "	50	.040		3 "	70	.144
	12 M.	75	.047		5 "	100	.091
	1 P. M.	85	.042		7 "	50	.116
	2 "	75	.063		12 hr.	150	.151
	3 "	65	.072		9 A. M.	20	.003
	4 "	50	.038		11 "	70	.074
	5 "	120	.060		1 P. M.	50	.009
	6 " "	75	.042		3 "	50	.007
	12 hr.	1250	.499		5 "	100	.050
					7 "	90	.051
No. 28. B.D.	12 hr.	560	.610		12 hr.	450	.024
	8 A. M.	80	.088		9 A. M.		
	9 "	45	.049		11 "	40	.031
	10 "	50	.051		1 P. M.	80	.080
	11 "	30	.033		4 "	200	.156
	12 M.	45	.099		5 "	70	.119
	1 P. M.	40	.066		7 "	180	.417
	2 "	40	.055		12 hr.	600	.300
	3 "	30	.041		9 A. M.	50	.024
	4 "	35	.040		1 P. M.	80	.115
	5 "	45	.040		3 "	50	.083
	6 "	45	.035		5 "	220	.261
	7 "	50	.045		7 "	80	.078
	12 hr.	760	.418		12 hr.	630	.598

test. Wassermann test was negative. The family history showed a high incidence of diabetes. Table VIII presents the results of one test. Total C=95, P=50, F=180, T. G.=142.

CASE 28.—Miss B. D. Age seventeen, height 5′ 5″, weight 105 lbs. Metabolism=41%. The patient showed very definite toxic goiter. Table VIII presents one test on the Standard Diet. Breakfast at 8 A. M., lunch at 12:30 and supper at 6 P. M. This case illustrates the lack of correlation of the "breaks" with the food ingestion.

CASE 29.—Mr. C. M. Age fifty-four, weight 48.5 kg., height 176 cm. A very definite case of hyperthyroidism. Basal metabolism = +55%. Table VIII gives the results of speci- by 2. This case illustrates how variable such cases are with respect to sugar wastage.

DISCUSSION

Kast, Croll and Myers[3] found in 12 normal individuals an average of .96 grams sugar excreted in 24 hours. Neuwirth[4] found .941 grams average in 26 normals while Folin and Berglund[5] found 1.203 grams in one normal. Our results show an average of 1.015 grams for 10 normals, 72 analyses being involved in the average.

Kast, Croll and Myers[3] in an extended investigation found only slight variations in the total sugar in the 24 hour specimen under greatly varying pathological conditions. Our own experience amply corroborates this work. We have therefore felt that little could be gained from a further pursuance of this line of study.

The curve of hourly sugar secretion suggested itself as a possible means of determining the state of sugar metabolism. As has been previously pointed out, peaks may occur in this curve which are entirely obliterated by compensatory valleys thus producing a combined specimen that is apparently not abnormal.

Empirically we have found that excursions of the hourly sugar curve above the 90 to 110 mg. level may be considered indication of abnormal carbohydrate metabolism. Individuals whom we have every reason to suspect as being entirely normal do not exhibit the so-called "breaks" or abnormal excursions of the sugar curve.

Consideration of the curves of the mild or suspected diabetics reveals how easily these cases might be overlooked by the single and 24 hour combined specimen tests. It would seem to be purely a matter of chance whether the examination was made during a break, in a valley or a composite of the two.

It is believed that the ability to detect latent, borderline or mild diabetes depends on the determination of the picture of hourly sugar secretion under the varying conditions of the patient's life. Certain cases (No. 1, Mr. S., as an example) so long as normal exercise was maintained kept his sugar curve normal in form but when subjected to excessive mental strain, general nervousness, etc.,—the result is a "break." Possibly the normal individual might do the same under very excessively abnormal conditions, but when one considers the form of the curve in connection with the clinical syndrome exhibited, little doubt is left as to the status of the case.

It would indeed be rash to claim that all hourly sugar wastage above the 90 to 110 mg. level proved the existence of diabetes mellitus. It is well known that pathological sugar excretions may be due to such conditions as hyperthyroidism, liver disorders, nervousness, etc. We have not in an examination of hyperthyroid cases found the type of curve characteristic of diabetics. In general it may be said that the borderline or mild diabetic exhibit "breaks" shortly after meals whereas, if a "break" occurs at all in hyperthyroid cases, it apparently has no relation to food ingestion.

Diet in the case of normal individuals so long as it is not excessively abnormal does not appear to play as important a rôle as might be expected. Certainly after food ingestion there is an increase in normal urine sugar secretion as Benedict, Osterberg and Neuwirth have shown. We have been able to find no proportionality between the height of the peak and the quality and quantity of food ingested. These peaks are generally followed by compensatory falls in this manner producing approximately a constant level of sugar excretion.

Diet in cases where diabetes is involved is a far more important matter. In such cases ¼ to ½ hour after meals the sugar secretion rises sharply and the rise may show some proportionality to the total glucose content of the foodstuffs ingested.

A comparison of this test with the ordinary glucose tolerance test may bring certain points of interest.

Gray[6] has shown in a statistical analysis of a very large quantity of published data that in patients clinically normal the fasting blood sugar may

vary from .04 to .16 per cent, the average being .09 to .10 per cent. After the ingestion of 100 grams of glucose the peak may vary from .14 per cent to .28 per cent.

With regard to the quantity of glucose ingested for the tolerance test Gray states, "The highest peak with the smallest dose of glucose is as great as the average peak for the largest dose of glucose. So it seems fairly reasonable to say that curves vary at least as much owing to individuals as owing to the size of the dose." Since Benedict, Osterberg and Neuwirth[2] have shown the marked influence of small amounts of food ingested along with the glucose it makes one feel, at least for borderline cases, the results of such a test would be decidedly doubtful.

Hamman and Hirschman[7] state that the duration of the glucose reaction is a more important index of the severity of the diabetes than is the height of the curve.

Gray further states, "Hence, it is conspicuous that a normal fasting blood sugar by no means excluded the presence of diabetes, and that the entire curve in a diabetic may be normal."

Our data amply confirms this statement. In all our borderline cases the fasting blood sugars and glucose tolerance tests have been entirely normal whereas the hourly sugar examination has demonstrated "break" after "break" in the sugar wastage.

Further we must recognize what an excessively abnormal condition is induced by the ingestion of 75 to 100 grams of glucose. Kawachi,[8] Martius,[9] Allen,[10] Ohler,[11] and Gray,[6] have sounded the warning against the danger to a subnormal pancreas of the use of the ordinary glucose tolerance test. Joslin and many others now use this test with great caution if at all.

We must also remember that the patient is subjected to a rather severe nervous strain, not only from the fact that the test is ordinarily conducted in the hospital, but also from the fear and pain involved in vein puncture for blood samples. The hourly urinary test may and should be conducted under the varying conditions of the patient's normal environment.

The hourly sugar curve gives us a complete picture of the progress of a patient so-called "sugar free." The curves presented will show how closely the sugar curve of a severe diabetic, properly treated with insulin, may be made to approximate that of the normal individual. Using the ordinary means of sugar determination, once the patient is desugarized, we must proceed in the dark. The normal sugar determination is applicable where the other tests are no longer available. The hourly curve offers the additional advantage of detecting "breaks" in the sugar metabolism. "These "breaks" may and should be covered by proper regulation of the insulin dosage and dietary therapeusis until by proper adjustment of dosage and diet, the hourly sugar curve becomes normal in form.

In the normal urine sugar we have not a picture of the momentary state of the sugar metabolism, but a 24 hour picture, after the great equalizer, the kidney, has played its part.

The dangers of insulin overdosage are well known to the users of insulin. The normal urine sugar method offers a means of determining the point where the danger zone of hypoglycemia is being approached. Our

results seem to demonstrate that a fall below the 30 mg. level *in a patient undergoing insulin treatment* should be regarded with considerable suspicion. As we have previously pointed out the amount of insulin required to reduce "normal urine sugar" to a dangerously low level is far in excess of that required to reduce pathological glucose wastage. This is indeed fortunate for were it not the case a patient would no sooner become sugar free than a hypoglycemic reaction would set in.

Hypoglycemic reactions are always marked by a powerful diuresis hence the total quantity of sugar excreted, unless this figure is calculated back to a normal basis for urine volume, may not indicate deficient blood sugar.

The Benedict, Osterberg test may be easily modified to give a method that could easily be run by patients. We have tried with success the following: Two c.c. urine plus 1 c.c. .6 per cent picric acid plus ½ c.c. .5 per cent NaOH plus 5 drops 50 per cent acetone mixed in an ordinary 20 c.c. test tube. The contents boiled 15 seconds and filled to a file scratch at 10 c.c. These tubes are then compared with permanent picramic acid standards.

Another phase and possibly the most important one of the normal urine sugar question is the plan of treatment to be followed with these borderline cases. It is believed that the method here described will detect a great many cases formerly overlooked. In one case, No. 30, J. B., who had a normal fasting blood sugar and glucose tolerance test, but exhibited pathological breaks according to our conception, we have given insulin. Fig. 7 shows quite definitely that the hourly sugar curve quickly became normal. Whether such patients had better be kept on a reduced diet without insulin or with insulin is a question for the future to decide.

In conclusion I wish to express my indebtedness to Dr. G. H. A. Clowes for advice and suggestions in the conduct of the work, to Mr. W. O. Rader for assistance in carrying out the laboratory work, to Drs. J. A. MacDonald, Louis Burckhardt, C. L. Rudesill and J. H. Warvel for providing clinical material, and to Miss Michael and Miss Thompson for cooperation on the clinical side.

SUMMARY

1. The hourly urine sugar curve has been determined in (1) Normal individuals; (2) Borderline diabetics; (3) Severe diabetics under insulin treatment; (4) Renal diabetes; (5) Borderline glycosuria under insulin treatment; (6) Hyperthyroid cases.

2. The use of insulin in borderline glycosuria has been briefly considered.

3. A standard technic has been described for the determination of hourly sugar curve.

4. It is believed that an examination of the hourly sugar curve will demonstrate cases of mildly pathological sugar metabolism that would be overlooked by the ordinary tests for such conditions.

5. A comparison of this test with the glucose tolerance test we believe demonstrates that in many ways it is very superior.

6. The method on the one hand detects abnormally high sugar wastage

and on the other warns of dangerously low sugar secretion, hence offers an almost ideal method for the control of cases of diabetes under insulin treatment.

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THE SIGNIFICANCE OF NEGATIVE RESULTS IN BLOOD CULTURES*

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THE SIGNIFICANCE OF NEGATIVE RESULTS IN BLOOD CULTURES

THE literature contains many reports of the bacteriologic examinations of the blood, and various infections have been studied in this way. Following is a list of the more important diseases in which positive results have been obtained: typhoid and paratyphoid fevers, pneumonia, infectious endocarditis, erysipelas, postpartum infections, cholecystitis, pyelitis, pyosalpinx, otitic infections, local infections and abscesses in various parts of the body, osteomyelitis, glanders, general cryptogenetic infections, certain cases of diphtheria, and in many of the obscure febrile cases so frequently seen in our hospital wards.

The usefulness of the bacteriologic examination of the blood in many infectious diseases is self-evident. Probably no other single method of diagnosis has yet been devised that furnishes of itself so definite and clear diagnosis as does this method. Its usefulness is, to be sure, limited to certain kinds of cases, but these cases are numerous and are often extremely difficult or impossible to diagnose by any other means.

While the literature upon the significance of positive blood cultures is voluminous, it contains no experimental work upon the possible meaning of negative blood cultures that meets modern bacteriologic requirements. The relatively large number of cases reported as giving a negative blood culture have not yet been explained by experimental evidence. Table I shows some of the reported cases which illustrate the importance of positive findings as well as the importance of knowing the meaning of the large percentage of negative findings.

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Table I shows that of a total of 2,284 cases, 1,514 cases (or 66.29 per cent) were positive, while 770 cases (or 33.72 per cent) were negative. The examinations were made at various stages of the diseases and by different methods. What does this large percentage of negative results mean? To answer this question, several factors must be taken in consideration. A few of the more important ones are here considered:

TABLE I

SOME REPORTED CASES

NO.	AUTHORS	ORGANISM	NUMBER OF CASES	POSITIVE	NEGATIVE
1	Auerbach and Unger	B. Typhosus	10	7	3
2	Bosquet	" "	83	83	0
3	Berri	" "	13	7	6
4	Brion and Kayser	" "	233	153	80
5	Cole	" "	15	11	4
6	Courmont and Lesieur	" "	37	37	0
7	Castellani	" "	14	11	3
8	Coleman and Buxton	" "	123	81	42
9	Duffy	" "	88	62	26
10	Epstein	" "	230	170	60
11	Eppenstein and Korte	" "	6	5	1
12	Fox	" "	14	1	13
13	Fornet	" "	19	14	5
14	Hewlett	" "	25	21	4
15	Hirsh	" "	97	75	22
16	Harrison	" "	8	5	3
17	Janesco	" "	19	8	11
18	Jochmann	" "	30	25	5
19	Kerr and Harris	" "	56	31	25
20	Kuehman	" "	21	9	12
21	Korte and Sternberg	" "	22	22	0
22	Kayser	" "	75	50	25
23	Loiseleur	" "	65	63	2
24	Memmi	" "	30	18	12
25	Perquis	" "	40	30	10
26	Ruediger	" "	32	20	12
27	Rolly	" "	50	43	7
28	Richard	" "	50	44	6
29	Rusta	" "	12	12	0
30	Schottmaeller	" "	119	98	21
31	Todd	" "	23	17	6
32	Trappe	" "	38	25	13
33	Widal	" "	25	17	8
34	Warfield	" "	48	33	15
35	Dul and Wright	Streptococci	57	16	41
36	Libman and Celler	"	30	23	7
37	Spassokukotsky	"	81	52	29
38	Raffaelli	Meningococci	22	20	2
39	Ryttenberg	Various bacteria	324	87	237
			2,284	1,514	770

1. The bactericidal effect of the serum introduced into the culture media with each sample of blood.

2. Number of organisms in infected blood in various pathologic conditions.

3. The viability of different bacteria.

4. Infection not due to bacteria.

Bactericidal Effect of Serum.—Much of the difficulty hitherto experienced

in cultivating the organisms found in the blood has been attributed to the bactericidal power of the blood. To overcome this Castellani[1] used large quantities of bouillon, and obtained positive results in 78 per cent of the cases of typhoid fever; Schottmüller,[2] however, used agar, the blood being present in the proportion of 1 to 3 in the medium and obtained positive results in 81 per cent of the cases in typhoid fever. Numerous other methods

NO.	QUANTITY OF BLOOD IN EACH PLATE	NUMBER OF COLONIES PER PLATE AT DIFFERENT INTERVALS						
		0 MIN.	15 MIN.	30 MIN.	1 HR.	2 HRS.	3 HRS.	4 HRS.
1	0.10 c.c.	39	35	107	138	115	195	324
2	0.09 "	12	11	69	125	108	150	208
3	0.08 "	18	10	52	104	97	133	276
4	0.07 "	14	8	15	118	84	101	312
5	0.06 "	4	7	14	102	79	86	121
6	0.05 "	0	3	15	88	63	69	100
7	0.04 "	6	5	8	61	31	57	69
8	0.03 "	3	0	14	59	45	49	52
9	0.02 "	0	1	4	36	13	12	45
10	0.01 "	0	0	0	27	16	14	18

have been employed by different investigators. Lemiere[3] was successful with cultures made from defibrinated blood of a typhoid fever patient. Muller and Graef[4] obtained growth of the B. typhosus in the fibrin net-work of clotted blood. Klodnitsky[5] succeeded in growing the typhoid bacillus from blood laked in ordinary sterile water. Epstein[6] found multiplication of the typhoid B. in oxalated blood in twenty-three out of twenty-five cultures without the addition of any nutrient material.

NO.	QUANTITY OF BLOOD IN EACH PLATE	NUMBER OF COLONIES PER PLATE AT DIFFERENT INTERVALS						
		0 MIN.	15 MIN.	30 MIN.	1 HR.	2 HRS.	3 HRS.	4 HRS.
1	0.10 c.c.	800	1,000	1,100	1,100	1,200	*	*
2	0.09 "	750	900	1,000	1,000	1,200	1,200	*
3	0.08 "	675	850	1,000	1,000	1,100	1,100	1,200
4	0.07 "	412	834	900	900	1,000	900	1,000
5	0.06 "	283	417	948	950	900	800	739
6	0.05 "	191	426	812	623	876	734	745
7	0.04 "	200	350	700	800	634	856	768
8	0.03 "	5	312	634	54	456	612	712
9	0.02 "	57	234	65	75	87	303	703
10	0.01 "	48	95	76	96	18	24	494

*Too many for accurate count.

From these data it will be seen that the claim so frequently made that the failure of the bacteria to grow is wholly due to the continuation of the bactericidal action of the blood (in vitro) is not supported by experience, and has been considerably overrated. This view gains support from the fact that bacteria multiply in defibrinated, oxalated, laked and clotted blood without the addition of any nutrient medium.

The work of Eppenstein and Korte, and later of Epstein, as well as my own experience, indicate that the B. typhosus, B. coli, B. mucosus capsulatus, most streptococci, staphylococci, and pneumoocci, B. mallei, resist the bactericidal action of the blood of the host and thus are not inhibited by any

bactericidal effect of the serum but tend to multiply. The method of adding a few drops of blood serum to broth for increasing viability and to improve growth of attenuated organisms is commonly employed. The following experiments will illustrate the above facts.

Experiment 1.—A loopful of a 20-hour broth culture of streptococcus hemolyticus was introduced into 10 c.c. sterile human blood. The following series of plates were poured at different intervals of time. During the four hours, the blood remained at room temperature (summer).

Experiment 2.—Six drops of sterile human blood serum was added to 10 c.c. sterile broth. This tube was inoculated with the organism used in the first experiment. After 20 hours' incubation, a loopful of this culture was introduced into 10 c.c. sterile human defibrinated blood. The following series of plates were poured at different intervals of time. During the four hours the blood remained at room temperature (summer).

It will be noticed that the number of organisms increased steadily the longer they were allowed to grow in the blood, and that they are more numerous in the table of Experiment 2 in which is the report of the culture containing six drops of serum. After the four hours, I incubated both tubes for twenty hours and then poured a series of ten plates with different quantities of blood from each tube. The number of organisms in each plate were so numerous that it was impossible to count them, proving that the streptococci grow well in human blood.

Taking the above facts into consideration, it becomes evident that in working with one or another method many of the real conditions underlying the success or the failure of blood-culture work have been overlooked.

Number of Organisms.—E. Libman[7] reported results obtained from studying 750 cases of bacteriemia by means of cultures. He found that "the number of organisms varied from one in fifteen c.c. up to 2676 to the c.c., or up to such a number that the colonies could not be counted." We also know that typhoid fever is a disease associated with relatively few organisms in the circulating blood, especially in the later period of the disease. Ryttenberg[8] found that twenty-six positive cultures representing one hundred and ninety c.c. of blood showed a total of one hundred and seventy-two colonies, an average of less than one colony per c.c. of blood. Of these twenty-six cultures the highest single count was about three colonies per c.c.; the lowest, one colony per ten c.c. of blood. We should also remember that some bacteriemias are caused by the liberation of bacterial emboli into the blood stream from some focus in the body, and that in these cases the blood may be periodically free from bacteria.

From the above data one sees that in a given sample of blood (usually not more than 10 c.c. and very frequently less than this quantity) containing very few organisms or a single organism, there is a large element of chance as to whether a given sample of blood will give a positive or negative culture.

To emphasize this element of chance in transient blood infections and bacteriemias associated with few organisms, I have performed the following experiment:

Experiment 3.—Six drops of sterile human blood serum was added to 10 c.c. sterile broth. This tube was inoculated with the same organism used in the first two experiments. After twenty hours' incubation, a loopful of this culture was introduced into 10 c.c. sterile human defibrinated blood. This tube is 1. A loopful of the blood of 1 was immediately introduced into another tube containing 10 c.c. human defibrinated blood. This tube is 2. The following series of plates were poured at different intervals of time.

NO.	QUANTITY OF BLOOD IN EACH PLATE	1		2	
		POURED INSTANTLY	POURED AFTER 24 HRS. INCUBATION	POURED INSTANTLY	POURED AFTER 24 HRS. INCUBATION
1	0.10 c.c.	276	*	3	*
2	0.09 "	112	*	0	*
3	0.08 "	161	*	0	*
4	0.07 "	204	*	0	1200
5	0.06 "	198	*	0	1000
6	0.05 "	107	*	0	*
7	0.04 "	91	1200	0	1000
8	0.03 "	98	1000	1	900
9	0.02 "	37	1200	0	800
10	0.01 "	12	1000	0	864

*Too many for accurate count.

The number of sterile plates in the above experiment illustrates the fact that the element of chance plays a very important rôle in cases where the number of organisms in the blood is not abundant. In 2, when plated instantly, only two positive results were obtained, while when the same culture was allowed to incubate for twenty-four hours, all the plates showed numerous colonies. From the above experiment we may, therefore, conclude: first, that larger quantities of blood and smaller dilutions must be used, and, second, that the sample of blood should be first incubated for twenty-four hours before plates are poured or samples distributed to different medias.

The Viability.—This factor is not a negligible one. One must select the most favorable medium for the organism suspected. This can be accomplished best by carefully considering the history of the case.

Again the disease affecting the patient may not be of bacterial origin, but the symptoms presented may be similar to those produced by a bacterial septicemia. Malaria forms a typical example of this type of infection.

If blood cultures are taken more frequently when clearly indicated, and the suggestions here made observed, I feel that the diagnosis of infectious diseases would be materially aided, for quite frequently it is impossible to make one without it. Positive blood cultures establish a diagnosis as but few other single procedures do.

SUMMARY

The bactericidal influence of the blood drawn for blood cultures has been overestimated.

The element of chance in obtaining a positive or negative blood culture plays an important rôle.

Larger quantities of blood and lower dilutions should be used in order

to offset this element of chance. High dilutions of the sample of blood are not essential.

At times there may be an advantage in first incubating the sample of blood for twenty-four hours before it is distributed to different nutrient media or poured on to plates.

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TOXICITY OF COCAIN AS INFLUENCED BY RATE OF ABSORPTION AND PRESENCE OF ADRENALIN*

By Ellison L. Ross, Ph.D., M.D., Chicago, Ill.

THE toxic reaction sometimes occurring with the clinical use of cocain, is often explained by saying that for some reason the drug was absorbed with unusual rapidity. As far as we have been able to ascertain no accurate data has been collected on this point. Consequently, we thought it sufficiently important to determine, within certain limits, the variation in the minimal lethal dose with the rate of introduction into the circulation.

There is a difference of opinion expressed in the literature concerning the influence of adrenalin on the toxicity of cocain. Allen[1] in his book on anesthesia states that "Adrenalin may prove a distinct disadvantage after cocain." Allen quotes J. M. Berry as believing that adrenalin increases the toxicity of cocain. He also quotes Thriss, Miles, Braun and Petrow as saying that adrenalin is of benefit to the patient after a toxic dose of cocain.

Buxton[2] in his book on anesthetics says that "even minute doses of adrenalin are said to cause unpleasant effects, e.g., giddiness, fainting and collapse."

Mortimer[3] discussed the existing difference of opinion on the advantages and disadvantages of adrenalin with cocain. He argues against the free use of adrenalin with cocain because of the possibility of extreme cardiac dilatation making contraction impossible. This mechanical factor we found to be present to a marked degree, as was shown in the blood pressure tracing of a number of animals that had been given cocain and adrenalin.

Harris[4] reported a death resulting from an injection of ½ of a grain of cocain with 8 to 10 minims of adrenalin. Those discussing the paper were divided in opinion, some thought the death due to the adrenalin and one thought it due to the cocain.

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Hatcher and Wilbert[5] state that "artificial respiration and injection of epinephrin saved a certain number of animals after injection of doses of cocain that were 25 per cent larger than those subsequently required to cause death."

Sollmann[6] in referring to cocain says "the toxicity is greatly lessened by the addition of epinephrin."

Our work[7] strongly suggested to us that adrenalin increased the toxic effect of cocain. The great rise in arterial pressure and greater rise in intracranial venous pressure and strong stimulation of the vagus, produced by

TABLE I

VARIATION OF TOXICITY DUE TO RATE OF ADMINISTRATION OF COCAIN

CAT	RATE OF INJECTIONS GM. PER MINUTE	LETHAL DOSE COCAIN—GM. PER KILO.	
		RESPIRATION STOP	HEART STOP
27	.0115	.0114	.0208
28	.0115	.0157	.0249
29	.0115	.0114	.0181
1	.0057	.0144	.0212
2	.0057	.0168	.0190
3	.0057	.0141	.0181
32	.0028	.0195	.0214
33	.0028	.0225	.0263
35	.0028	.0196	.0215
40	.0230	.0156	.0422
41	.0230	.0165	.0387
42	.0230	.0128	.0267

TABLE II

VARIATION OF TOXICITY WITH RATE OF ADMINISTRATION OF COCAIN—AVERAGE

CATS	STRENGTH OF SOLUTION PER CENT COCAIN	RATE OF INJECTION GM. PER MIN.	LETHAL DOSE COCAIN—GM. PER KILO.	
			RESPIRATION STOP	HEART STOP
3	½	.0115	.0128	.0213
3	¼	.0057	.0151	.0194
3	⅛	.0028	.0208	.0231
3	1	.0230	.0150	.0359

cocain with adrenalin could hardly help being depressing. Therefore work was directed to determine whether adrenalin is an antidote for cocain poisoning or a substance increasing its toxicity.

EXPERIMENTAL WORK

Cats were used as subjects. They were given enough ether to quiet them and were then injected intraperitoneally with ¾ c.c. of a 25 per cent solution. of chloretone in olive oil, for each kilogram of body weight. The femoral vein was exposed and a canula inserted into it. Connected with the canula there was a motor driven machine which injected the solution at the uniform rate of 2.3 c.c. per minute.

The first point to be determined was the effect of the rate of injection on the lethal dose. The first three cats were given a 1 per cent solution of cocain in normal salt solution. The lethal dose was measured by the time required to stop respiration and heart beat. The second three cats were given a half per cent solution of cocain. The third group was given a quar-

ter per cent solution and the fourth group an eighth per cent solution. The results are given in Table I. The average results are given in Table II.

The second part of the problem was to determine whether adrenalin increased or decreased the lethal dose of cocain. Seven groups of three cats each were used for this purpose. The first group of cats were given normal salt solution containing one-fourth per cent cocain and 0.2 per cent adrenalin

TABLE III

EFFECT OF ADRENALIN ON TOXICITY OF COCAIN

CAT	PER CENT ADREN.—WITH COCAIN		LETHAL DOSE COCAIN—GM. PER KILO.	
			RESPIRATION STOP	HEART STOP
1	None	¼%	.0144	.0212
2	None	"	.0168	.0190
3	None	"	.0141	.0181
4	0.2	"	.0144	.0194
5	0.2	"	.0175	.0213
6	0.2	"	.0139	.0190
7	0.4	"	.0126	.0149
8	0.4	"	.0173	.0219
9	0.4	"	.0125	.0227
10	1.0	"	.0117	.0165
11	1.0	"	.0089	.0115
12	1.0	"	.0104	.0137
13	5.0	"	.0090	.0116
14	5.0	"	.0080	.0109
15	5.0	"	.0060	.0110
16	10.0	"	.0065	.0106
17	10.0	"	.0051	.0096
18	10.0	"	.0073	.0172
19	None	⅛%	.0195	.0214
20	None	"	.0225	.0263
21	None	"	.0196	.0215
35	1.0	"	.0093	.0093
36	1.0	"	.0144	.0154
38	1.0	"	.0111	.0115

TABLE IV

EFFECT OF ADRENALIN ON TOXICITY OF COCAIN—AVERAGE

PER CENT ADRENLIN WITH COCAIN		LETHAL DOSE OF COCAIN—GRAMS PER KILO.	
		RESPIRATION STOP	HEART STOP
0.00	¼	0.0151	0.0194
0.20	¼	0.0153	0.0199
0.40	¼	0.0141	0.0198
1.00	¼	0.0103	0.0139
5.00	¼	0.0077	0.0107
10.00	¼	0.0063	0.0129
0.00	⅛	0.0208	0.0231
1.00	⅛	0.0116	0.0121

(1:1000). The second group received the same except that the solution contained 0.4 per cent adrenalin. The third group got 1.0 per cent adrenalin. The fourth group was given 5.0 per cent adrenalin with cocain and the fifth group 10 per cent adrenalin with cocain. The sixth group received 15 per cent adrenalin and no cocain. The seventh group was given 1.0 per cent adrenalin and one-eighth per cent cocain. These results are give in Table III. The average results are given in Table IV.

DISCUSSION

The measurement of the minimal lethal dose was made by determining the moment of the stoppage of respiration and also of the heart. It was, at first, thought that the failure of the heart would be the best indication that injection of the lethal dose had been completed. However, it was found that the actual time of cessation of beating could not be determined without exposure of the heart and that the heart-beat could not be detected by touch or vision equally well in all individuals. Consequently, the time when regular respiration stopped was considered as the best indicator that the lethal dose had been administered. The dose calculated from the time of the arrest of the heart-beat is included here chiefly as a check on the other.

In Table I, it may be noted that there was a rather wide variation between individuals of the group. This variation is to be expected as it is a well-known fact that among people there is a wide range of susceptibility to cocain.

Table II includes the average of the results of the group of animals given the cocain at different rates. As the concentration of the solution of cocain decreased from 1 to ⅛ per cent, or as the rate of injection of cocain decreased from .0230 to .0028 grams per minute, the lethal dose first dropped and then gradually raised to its highest point at ⅛ per cent concentration. The lethal dose for the 1 per cent solution was higher than that for the ½ per cent solution, because the rate of introduction was greater than the rate at which the toxic action of cocain developed in these animals. In other words, when the respiration stopped in the first group of cats there must have been a certain amount of cocain in those cats that had not had time to take any part in killing them. The increasing lethal dose with a decreasing rate of introduction of cocain, from the ½ per cent to ⅛ per cent, was probably due to the elimination of a part of the cocain by the time respiration stopped. According to measurements made with reference to respiration, ½ per cent cocain solution injected at the rate of 2.3 c.c. per minute seemed to be the most effective. There seemed to be with this rate of introduction the least amount of eliminated cocain and the least amount of cocain unutilized. Therefore, for cats weighing between two and three kilos, the minimal lethal dose under the described conditions is .0125 grams of cocain hydrochloride per kilogram of body weight. This agrees very closely with the M.F.D. for rabbits as stated by Sollman[8] which is given as .01 to .022 grams per kilo.

The effect of adrenalin on the lethal dose of cocain is shown for individuals in Table III. As for cocain alone, there was a wide individual variation for the combination of adrenalin and cocain. The average group results are given in Table IV, from which a comparison of the drug effects can best be made. Inasmuch as the two cats, injected with 15 per cent adrenalin for 35 to 40 minutes at the rate of 2.3 c.c. per minute, were apparently uninjured, it was considered that the toxic effect of adrenalin alone, when in concentrations of 10 per cent or less and injected for periods of less than 15 minutes, was negligible. The addition to ¼ per cent cocain solution of increasing amounts of adrenalin from .4 to 10 per cent gradually increased the toxicity

of the solution. The addition of .2 per cent adrenalin seemed to have little or no effect on the toxicity of the cocain solution. The addition of .4 per cent adrenalin increased the toxicity only about 7 per cent. However, the addition of 1, 5, and 10 per cent of adrenalin increased the toxicity of the mixtures approximately 47, 95, and 140 per cent.

The effect of adding 1 per cent adrenalin to a ⅛ per cent cocain solution was determined. Without adrenalin the lethal dose of cocain was .0208 grams per kilo and with the adrenalin it was .0116. This increase in toxicity of the solution was approximately 79 per cent. It is an interesting fact that the minimal lethal dose of cocain in a 1 per cent adrenalin is approximately the same whether the cocain is ⅛ or ¼ per cent. This means simply that, other things being equal, the increased amount of adrenalin injected with the ⅛ per cent cocain solution made up for the loss in toxicity due to slower rate of introduction of the cocain in the ⅛ per cent solution.

SUMMARY AND CONCLUSIONS

Cats were given a light dose of chloretone. Cocain hydrochloride in concentrations varying from ⅛ to 1 per cent in normal salt solution was injected mechanically into the leg veins. The rates of introduction of the cocain varied from .0028 to .0230 grams per minute, per kilogram of body weight. As the rate of introduction of cocain increased the minimal lethal dose of cocain first decreased and then gradually increased up to the end of the series. The minimal lethal dose of cocain hydrochloride for chloretoned cats under these conditions is .0128 grams of cocain per kilo of body weight.

A series of groups of cats were injected with a ¼ per cent solution of cocain hydrochloride to which was added increasing amounts of adrenalin ranging from .2 to 10 per cent. With the increase in the concentration of adrenalin there was a gradual increase from 7 to 140 per cent in the toxicity of the mixture. In addition to this series a group of animals was given a normal saline solution containing 1 per cent adrenalin and ⅛ per cent cocain hydrochloride. It was found that the adrenalin increased the toxicity of the solution 79 per cent. Adrenalin in a concentration of 15 per cent injected at a rate of 2.3 c.c. per minute could not be made to kill cats.

Briefly stated the conclusions are as follows:

1. The M.F.D. of cocain for cats varies with the rate of administration.

2. The absolute M.F.D. of cocain hydrochloride for chloretoned cats is .0128 grams per kilo of body weight.

3. Adrenalin markedly increases the toxicity of cocain.

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A METHOD FOR THE ISOLATION OF WHITE BLOOD CELLS*

By Paul Szilard, M.D.

INTRODUCTION

EXPERIMENTAL work with white blood corpuscles is rendered exceedingly difficult and in many instances impossible by the circumstance that we do not possess a reliable method to separate the cells in bulk from other tissue. The generally applied method, i.e., the injection of a sterile solution of aleuronat into the abdominal cavity of a guinea pig, produces a pathologic condition which may well affect the white cells, while furthermore, the exudate which gathers in the abdominal cavity consists almost entirely of polynuclear neutrophile granulated leucocytes, and very few monocytes and lymphocytes are to be found. White cells may also be obtained by differential centrifugation, but always some red cells and thrombocytes are mixed therewith. The need for a reliable method to obtain leucocytes is shown by the utilization that has been made of various fluids in which they are abundant, i.e., the pus of fresh abscess (Neufeld and Rimpau), gonorrheal secretion from the urethra (Loewenstein), cystitic urine (Loewenstein), meningitic exudate (Davis), tuberculous sputum (Loewenstein).

The writer has worked out a simple means whereby white blood cells can be isolated almost quantitatively from a small volume of blood.

The essential point of the procedure is the destruction of the red blood corpuscles and the thrombocytes in a manner which will leave the white cells unimpaired. Acetic acid, usually applied for dissolving red blood corpuscles, is useless here, for two reasons: First, it injures the white blood cells inasmuch as it coagulates the proteids of their nuclei; and in addition, after hemolysis and centrifugation, the sediment contains not only the white cells, but also the remains of the erythrocytes. Hemolysis with distilled water is useless for the same reason.

Experiments were undertaken with acids in different concentrations, i.e., HCl, HNO_3, H_2SO_4, and with organic acids such as citric, tartaric, formic acid, etc.

While testing various combinations it was observed that in a certain mixture of acetic and tartaric acid the white blood cells had scarcely suffered at all; their nucleoproteids had undergone relatively little coagulation and the number of destroyed cells was small. It seemed probable that the tartaric acid served partly to reduce the coagulating effect of the acetic acid.

An attempt was now made to neutralize the free acid remaining after hemolysis had been accomplished by the combined acetic and tartaric acids.

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The result was encouraging, for although some red blood corpuscles were present in the sediment, their number was small. When the mixture was rendered not merely neutral but slightly alkaline, only white blood cells were found in the deposit after centrifugation.

PROCEDURE

The following are the solutions required:

1. 2.5 per cent solution of acetic acid.
2. 2 " " " " tartaric acid.
3. 2 " " " " potassium hydroxide.
4. Locke's solution.

Blood taken from the cubital vein by puncture or by syringe is defibrinated by gentle shaking with glass beads. Twenty-five to 30 c.c. will yield a goodly quantity of white blood cells. The blood should if possible be used

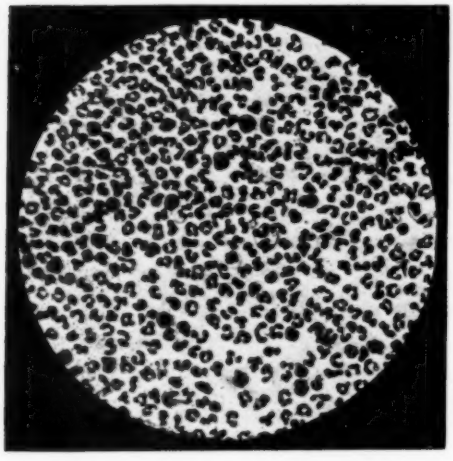

Fig. 1.—The white blood cells of a healthy man isolated by the above described method. Zeiss apparatus. Apochrom. object.: 8 mm. Project. ocul.: 2 mm. Tubus length: 160 mm.

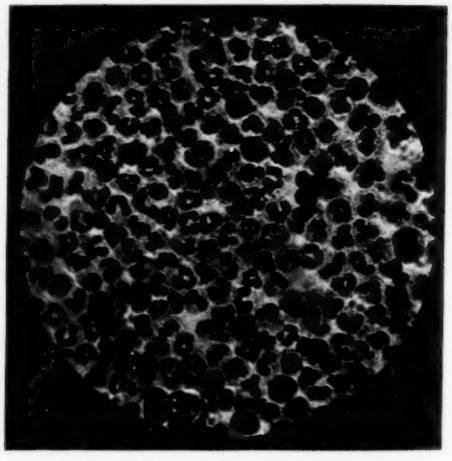

Fig. 2.—The same as Fig. 1. Apochrom. object.: 4 mm. Project. ocul.: 2 mm. Tubus length: 160 mm.

immediately after defibrination, and under no circumstances should it be allowed to stand longer than from 2 to 3 hours before using.

A mixture of acetic and tartaric acid in the proportion of 4 : 1 is employed for hemolysis. Of this mixture only the quantity required for complete hemolysis should be employed. This minimal amount of acid can be determined by preliminary experiments. In my experience, 12 c.c. of acetic and 3 c.c. of tartaric acid are required for 10 c.c. of blood.

The quantity of alkali necessary to neutralize the acid mixture to phenolphthalein should also be determined, and for each 10 c.c. of blood 1 c.c. more than the quantity of alkali required for neutralization will be needed. If any of the stock solution deteriorates through bacterial infection—and this is frequently the case with the tartaric acid—it must be titrated again.

The acid mixture is poured quickly into the blood with which it is

mixed by gentle rotation until complete hemolysis has taken place, as indicated by the varnish-like appearance of the laked blood. A too prolonged treatment with acid is undesirable, since it causes the white cells to deteriorate. The alkali is now poured rapidly into the tube and well mixed, and the whole transferred to a centrifuge tube. If the mixture is brown in color or shows turbidity when held against the light, it should be discarded. This happens when an insufficient amount of alkali has been employed.

The centrifugation should not be continued for longer than five minutes, as it is injurious to the white cells. But more important than the period of centrifugation is the rate of speed, which should not exceed 1,000 to 1,500 revolutions per minute, since very rapid centrifugation damages the cells.

After centrifugation the cells will be seen at the bottom of the tube as a white agglutinated mass, while the supernatant fluid is homogeneous, transparent, and bright purplish-red in color. It should be poured off and the sediment suspended in Locke's solution and washed with it once or twice at a low speed of the centrifuge. Ordinary sodium chloride solution should not be employed for washing, as it is injurious to the leucocytes.

When a portion of the washed cell sediment is spread on a slide and stained with May Grünwald and Giemsa stains by Pappenheim's method, only an occasional red cell is to be seen. At first sight there would appear to be present a greater number of young leucocytes and monocytes than we find in the microscopic film made from blood taken from the tip of the finger. But that is an erroneous impression, due to the great number of cells massed together. A differential count shows the usual proportion to exist amongst the leucocytes. Typical pictures are shown in Figs. 1 and 2.

When the white corpuscles are suspended in a little serum, or better, in their own plasma, and incubated for from ½ to one hour in a hanging drop, their ameboid movement is clearly visible—evidence that the cells are alive. Directly after centrifugation, no movement is seen or is seen only rarely.

In experiments with living leucocytes great attention should be paid to the apparatus. Glassware, centrifuge tubes, solutions, etc., should be kept throughout in the thermostat at 37° C. For microscopic examination a warm stage is recommended, for the leucocytes are rather sensitive to external influences. The blood if not used directly should also be kept in the thermostat, under no circumstances in the ice box. Great care should be paid to sterility.

Even under the best of circumstances, some 20 per cent to 30 per cent of the white cells are spoiled, on account of the coagulation of their nucleoproteids. The remaining white blood corpuscles can be kept alive for 24 hours or even longer; they are even capable of phagocytosis.

The method is equally suitable for the isolation of human and of animal white blood cells; but the quantity of acids and alkali required differs with the species. To hemolyze 10 c.c. defibrinated sheep's blood requires 8 c.c. of a 2.5 per cent solution of acetic acid plus 2 c.c. of a 2 per cent solution of

tartaric acid; for 10 c.c. of defibrinated horse's blood, 10 c.c. of acetic acid plus 2.5 c.c. of tartaric acid is needed; and for 10 c.c. defibrinated ox blood, 10 c.c. of acetic acid plus 2.5 c.c. of tartaric acid; while for 10 c.c. defibrinated swine's blood, 12 c.c. of acetic acid plus 3 c.c. of tartaric acid must be used. The quantity of a 2 per cent solution of potassium hydroxide must be varied to suit the case.

The technic of this simple method can be thoroughly mastered in the course of a few days. By it the plasmodium of malaria is readily obtained.

CLINICAL AND LABORATORY PROCEDURES IN PEDIATRICS

By A. Levinson, M.D., Chicago, Ill.

(*Continued from page* 588.)

Cerebrospinal Fluid

Indications for Removal of Fluid.—

For Diagnosis
- Suspicious meningitis
- Suspicious poliomyelitis
- Hemorrhage of the brain
- Neurosyphilis
- Coma
- Convulsions

For Treatment

(a) Relief of intracranial pressure
- Meningitis
- Meningism
- Poliomyelitis
- Encephalitis
- Hemorrhage of the brain
- Delirium
- Convulsions

(b) Intraspinal injections

1. Serum Treatment
   - Antimeningococcus
   - Pneumococcus Type I
   - Influenza
   - Poliomyelitis
   - Tetanus antitoxin
   - Horse serum
2. Chemicals
   - Neosalvarsan
   - Mercury
   - Optochin
   - Magnesium sulphate
   - Novocain
   - Adrenalin

(c) Miscellaneous
- General edema
- Diabetes insipidus

METHODS OF REMOVING FLUID

One of three routes may be used to withdraw cerebrospinal fluid from a human being: (1) Spinal, (2) Ventricular, (3) Cistern or occipito-atloid. Of these three routes, the spinal is the simplest and most advisable. Next to it is the ventricular route, and next to it, and the most dangerous route, is the cistern or occipito-atloid. Whenever possible, therefore, a spinal puncture should be done for the withdrawal of the cerebrospinal fluid from the body. Because of its importance, spinal puncture will be discussed first.

TECHNIC OF SPINAL PUNCTURE.—The needle for spinal puncture in children should be of a wide lumen, otherwise, the thick fluid often encountered in suppurative meningitis may occlude the opening of the needle. There are several makes of spinal puncture needles on the market, most of them being 2½ to 3 inches in length and 0.2 to 0.6 mm. in thickness. Each needle is fitted with a stylet. There are also needles with stopcocks made to fit various manometers used for measuring the pressure of the fluid.

The test tubes for collecting the fluid should be small, sterile and chemically clean, otherwise the interpretation of the results obtained by examination may be misleading.

The preparation for spinal puncture should be the same as for any other operation. The needle should be boiled, the patient's skin should be washed with alcohol and iodine and the physician should scrub his hands and wear gloves during the puncture.

The puncture should be done with the patient on a table or cart, a bed not being steady enough. All punctures should be performed with the patient lying down, preferably on his right side. The patient's body should be bent, so as to separate the intravertebral spaces. The needle should be introduced directly into the median line in very young children, and a few millimeters away from the median line in older children. The space of choice for the introduction of the needle is between the second and third interspace, although in children one may go one space higher without fear. A horizontal line drawn at the level of the crest of the ilium will usually strike the desired interspace.

After puncturing the skin, the needle should be directed forward and slightly upwards, until a snap is felt, which usually indicates the puncturing of the dura. The stylet should then be removed and the fluid, if obtainable, emptied into the test tubes. In case a manometer is used, the stopcock should be turned to prevent the escape of fluid, the manometer attached, and the pressure measured before the fluid is allowed to run into the test tubes.

It has been found best to use three or four test tubes for the collection of the fluid, so that if the patient moves around during the latter stage of the puncture and the fluid becomes bloody, as often happens, the first or second tube could still be used for examination. After the desired amount of fluid has been obtained, the stylet should be reintroduced into the needle, and the needle pulled out from the patient's body. The wound should be closed with collodion.

Rest in bed should be insisted upon after every spinal puncture. While

it does not always prevent headache, if it does occur, the headache is not so severe as when the patient is up and around.

FAILURES IN SPINAL PUNCTURE.—The two most important and most frequent failures are (1) inability to obtain fluid and (2) obtaining bloody fluid. While there are cases where there is very little or no fluid in the spinal canal, such as in marked atrophy of the spinal cord and in obstruction of the canal by a tumor, the average dry tap is due to the fact that the operator has not reached or has passed beyond the spinal canal. In very fleshy children it is hard to feel the intervertebral spaces. Failure to obtain fluid is therefore more frequent in fat than in slender children.

Fig. 23.—Photograph showing ventricular puncture in infant by way of the anterior fontanelle. Dark circular spot shows needle in position. (Front view.)

In deformities of the spine, due to rickets or tuberculosis, it may be impossible to reach the spinal canal. In such cases, it may be necessary either to introduce the needle obliquely to reach the spinal canal, or, to resort to a ventricular puncture.

Obtaining bloody fluid is possibly the most frequent mishap in spinal puncture. It happens to both the inexperienced and the experienced. The blood is due to injury produced to the plexus of veins in the canal. Once blood is obtained the fluid cannot be used for cell count or any chemical tests. It may, however, still be used for bacteriologic purposes. A Wassermann

test may be performed on bloody fluid, although at times the blood makes the fluid anticomplementary. If clear fluid is desired for examination, no new puncture should be done for several days after blood has been obtained, as it takes three days for blood to be absorbed from the spinal canal. However, when it is necessary to give serum intraspinally, blood obtained on spinal puncture does not counterindicate the procedure.

Death after spinal puncture has been reported in the literature. Death in those cases was seemingly due to the withdrawal of too great a quantity of fluid, thereby allowing parts of the brain to descend to the foramen magnum and become obstructed there. With the exception of a tumor of the

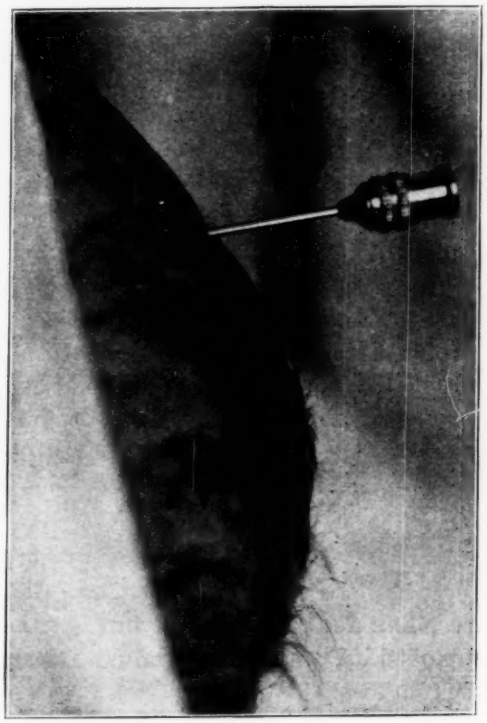

Fig. 24.—Photograph showing ventricular puncture in infant. (Side view.)

cerebellum, no condition counterindicates spinal puncture, the possibility of death by puncture being minimal. I have done many punctures in cases of brain tumor without a single complicating death.

Shock is not an infrequent complication. A hypodermic injection of atropine usually relieves it.

Injury to the aorta by spinal puncture has been reported, but is very uncommon. Breaking off the needle is not an infrequent complication in adults, but seldom occurs in children.

Headache after a spinal puncture is a common occurrence, but usually disappears in a day or two, especially if the patient stays in bed.

Radiating pain in the lower extremities takes place if filaments of nerves

have been touched in the spinal canal by the needle. The pain, however, does not last long.

Edema of the skin in the lumbar region has been observed after repeated punctures. The edema, however, subsides in a few days.

VENTRICULAR PUNCTURE.—*Indications.*—Ventricular puncture in infants is not associated with any danger, yet it should not be performed unless lumbar puncture has failed repeatedly. Where the latter has failed either for the purpose of the removal of cerebrospinal fluid or for the introduction of serum, ventricular puncture should be performed without hesitation.

Technic.—The hair around the anterior fontanelle should be shaved and alcohol and iodine applied. The operation proper varies with the age of the child. In infants the operation is very simple. In older children, in whom the anterior fontanelle is closed, the procedure is complicated and requires many surgical instruments.

The technic in infants is as follows: The patient is placed in the recumbent posture on a table, with the head at the end of the table. The head, shaved and washed with alcohol, is steadied by an assistant. A regular spinal puncture needle is now introduced a few millimeters to one side of the midline of the anterior fontanelle. The needle is directed forward and slightly downward to a depth of 1 to 1½ inches. In hydrocephalic children ½ inch suffices. The stylet is now removed and fluid is collected into one or more test tubes (Figs. 23 and 24). If no fluid is obtained, the needle should be withdrawn and reintroduced, but should not be manipulated unduly while in the brain, in order to avoid damage to the brain tissue. If no fluid is obtained by the fontanelle route, and if the bones of the skull are still separated, the needle may be introduced between the frontal and parietal bone 1 to 1½ inches deep.

CISTERN PUNCTURE

If both the spinal and ventricular routes have failed for the purpose of obtaining cerebrospinal fluid, or for the introduction of serum, cistern puncture may be employed. The technic, originally described by Wegeforth, Ayers and Easiek is as follows:

A spinal puncture needle is introduced into the midline of the back of the neck just above the spine of the axis. The glabella and the upper edge of the external auditory meatus may be used as a landmark for the insertion of the needle, for a plane passed through them to the back of the neck will pass also through the occipito-atloid ligament. In thin individuals a deep depression can be palpated between the occipital protuberance and the spine of the axis. This depression serves as another landmark. The needle is introduced at a depth of 3 to 5 cm., the average being 4 cm.

The preparation for the puncture and the collection of the fluid are the same as in spinal or ventricular punctures.

METHODS OF EXAMINATION

The fluid should be examined for physical, chemical, physiochemical, bacteriologic and immunologic alteration.

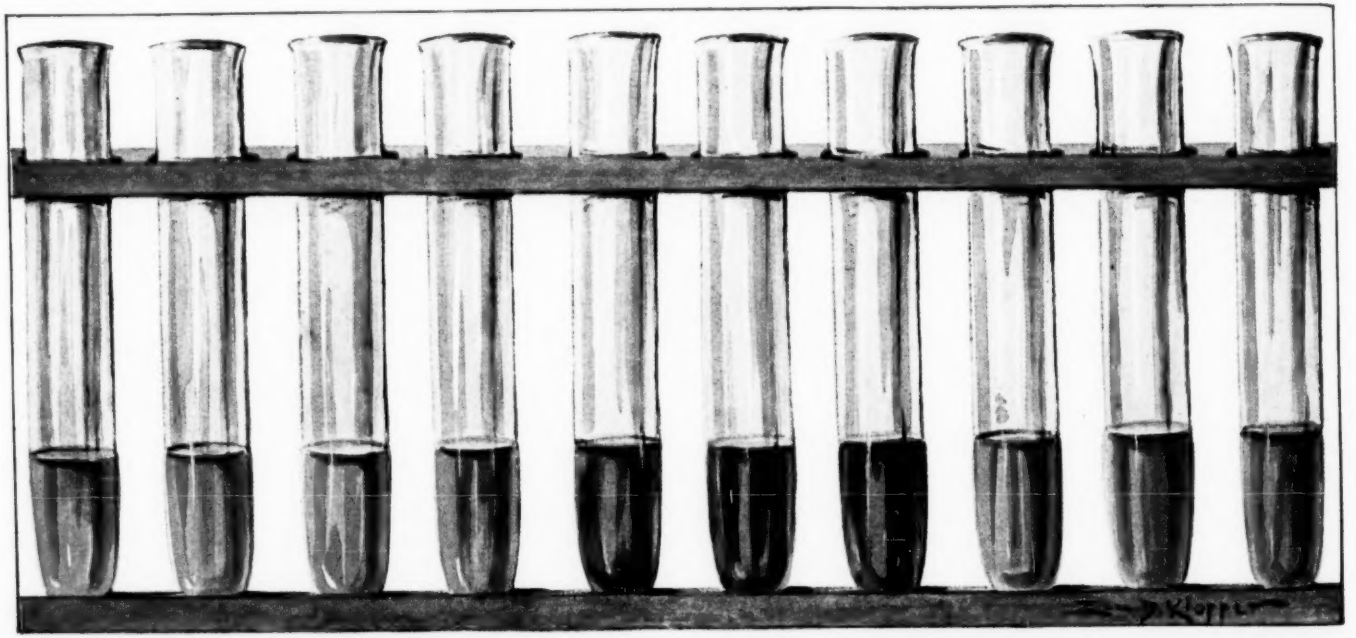

Fig. 25.—Lange gold chloride reaction in a case of tuberculous meningitis.

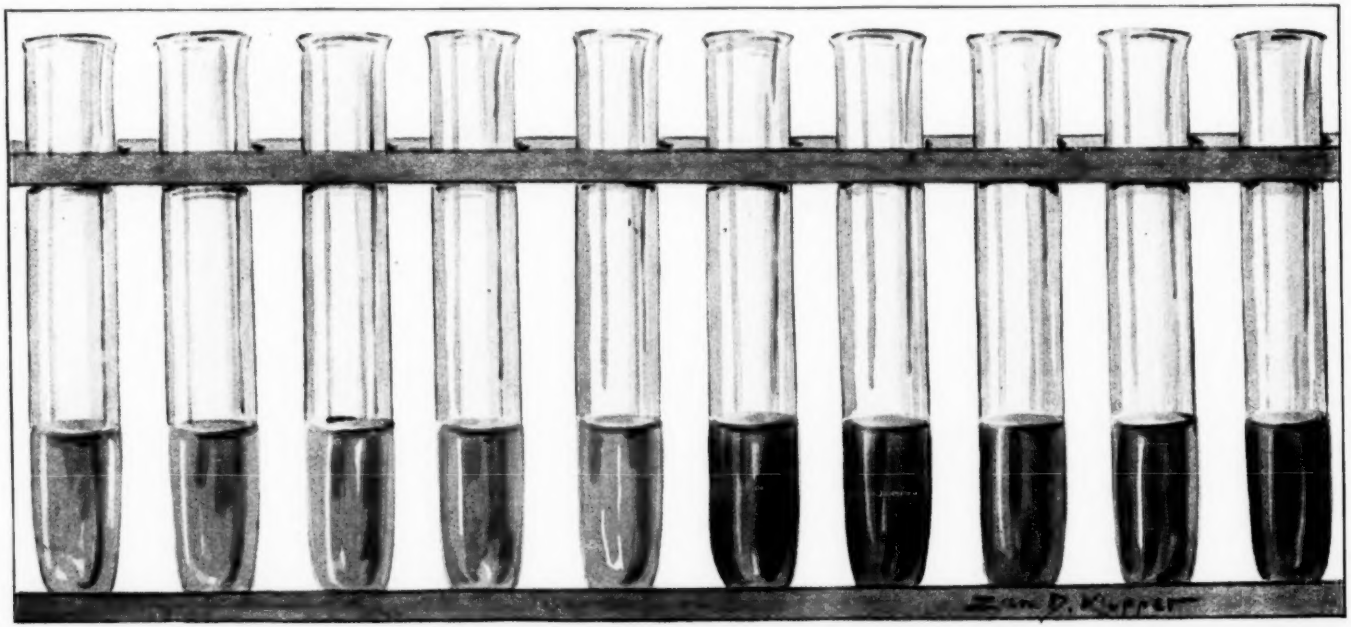

Fig. 26.—Lange gold chloride reaction in a case of meningococcus meningitis.

AMOUNT.—Normally, only five to ten c.c. of cerebrospinal fluid can be removed by spinal puncture. In nearly all pathologic cases, the amount of cerebrospinal fluid is increased. In acute infections, whether due to inflammation or only to irritation of the meninges, the amount is greatly increased and one can often remove as high as 30 to 40 c.c. in one sitting. In chronic inflammation of the meninges or of the brain, the amount is also increased. Only in tumor of the cord and in some cases of obstructive hydrocephalus is the amount decreased. Seldom does one see a case where no fluid at all can be removed from the spinal canal and which is not due to faulty technic. Such may be the case in tumor of the cord or in spina bifida.

PRESSURE.—Normally, the pressure of the cerebrospinal fluid, when measured as it escapes from the canal, is 40 to 90 mm. of water high in the recumbent posture in children. In acute infections or irritations of the meninges the pressure may go up as high as 300 or 400 mm. of water. In cases of obstruction of the cord, the pressure may be lessened.

COLOR.—Normal cerebrospinal fluid is colorless. Many pathologic conditions do not change the color of the fluid, such for instance is the case in encephalitis, poliomyelitis and tuberculous meningitis. In some conditions, however, the fluid changes color. In all suppurative meningitis for instance, the fluid is turbid. In jaundice, the fluid is greenish-yellow; in tumors of the cord, the fluid is deep yellow, and is known as xanthochromia. In hemorrhage of the brain, the fluid is bright or dark red, in the early stages, but may be colorless after a few weeks.

SEDIMENT OR PELLICLE.—Normal fluid forms no sediment when allowed to stand. In meningitis, however, a pellicle or sediment often forms in the fluid on standing. In suppurative forms of meningitis, the pellicle forms within a few minutes. In tuberculous meningitis, it usually takes 12 to 24 hours for the sediment to form.

GLOBULIN.—Normal fluid contains only a small amount of protein. All acute and chronic inflammation of the meninges increases the protein in the fluid.

The following are the most simple tests for the determination of the increase of globulin.

Pandy.—One drop of cerebrospinal fluid is added to one or two c.c. of a concentrated solution of carbolic acid (1 part phenol crystals to 15 parts of water). A bluish white cloud forms in the test tube if globulin is present in excess of normal. When mixed, the solution becomes turbid. If the globulin is not increased the solution remains clear.

Ross-Jones.—Two-tenths to 0.5 c.c. of a saturated ammonium sulphate solution is poured into a small test tube. An equal amount of cerebrospinal fluid is floated upon it by running it down the side of a slanted tube. A white ring develops in a few seconds to 2 or 3 minutes at the point of contact, if the globulin in the fluid is increased.

Noguchi.—Two-tenths c.c. of cerebrospinal fluid is poured into a small test tube, and 0.5 c.c. of a butyric acid solution (5 c.c. of butyric acid to 45 c.c. physiologic salt solution) is added to the fluid. The mixture is boiled for a

few seconds and 0.1 c.c. of NaOH (normal 4 per cent aqueous solution) is added to it and it is again boiled for a few seconds. If the globulin in the fluid is increased, a fine or coarsely granular, flocculent deposit forms in from one to ten minutes. If no coarse flocculi appear within two hours, even if a slight opalescence is present the globulin is not increased.

SUGAR.—Normally, cerebrospinal fluid contains 0.08 to 0.1 per cent of sugar. In suppurative meningitis, especially in the meningococcus form, the sugar is either decreased or absent from the fluid. An absence of sugar in the fluid, therefore indicates meningitis. Although not very accurate, Fehling's reduction test will answer the purpose.

THE LANGE GOLD CHLORIDE TEST.—The gold chloride test of Lange may be considered of great value in the diagnosis of pathological conditions of the cerebrospinal fluid. Normally, the fluid does not change the ruby red color of the original gold chloride solution. In luetic infections of the central nervous system, one or more of the first five tubes in the series, is changed in various degrees, from violet to colorless. In tuberculous meningitis the fifth, sixth and seventh tubes are usually affected. In suppurative meningitis one or more of the last five tubes change colors. (Figs. 25 and 26.)

The technic of making up the gold chloride solution is rather difficult, some solutions producing color changes even with normal fluids, and others producing no changes even with distinctly luetic fluids. Care must be taken to see that the solution is transparent, of neutral reaction, and that it is precipitated by 1.7 c.c. of 1 per cent NaCl solution in one hour. There are several modifications of the original Lange technic of preparing colloidal gold solution, but we believe the following technic to be very satisfactory.

The method is as follows: To 1000 c.c. of doubly distilled water, 10 c.c. of a 1 per cent gold chloride solution and 7 c.c. of a 2 per cent solution of potassium carbonate are added. The mixture is heated to 90° C., stirred vigorously and 5 c.c. of a 1 per cent formaldehyde solution is added. The solution should at once assume a red color.

The method of testing cerebrospinal fluid with the above solution is as follows: 0.2 c.c. of cerebrospinal fluid is introduced into the first one of a series of 10 test tubes containing 1 c.c. of 0.4 per cent sodium chloride. Ten dilutions of the cerebrospinal fluid are now made, by taking 1 c.c. of the first tube and transferring to the second, then 1 c.c. of the second and transferring to the third, etc., the dilutions thus ranging from 1 to 10 to 1 to 5120. An eleventh tube containing 1 c.c. of 0.4 per cent sodium chloride without cerebrospinal fluid may be used as a control. It is also advisable to run another gold chloride test on a fluid known to be normal. To each tube 5 c.c. of the colloidal gold reagent (1 per cent solution of gold chloride, 2 per cent solution of K_2CO_3, 1 per cent solution of formalin) is added.

CELLULAR ELEMENTS.—Normal fluid contains one to six cells per cubic mm. all of which are small lymphocytes. In infections of the meninges and occasionally in irritation of the meninges, the number of cells are increased. The more acute the infection, the greater the number of cells.

The type of cell differs with the pathologic condition. In tuberculous

TABLE XII

CEREBROSPINAL FLUID FINDINGS IN VARIOUS CONDITIONS

CONDITION	ORGANISM	COLOR	AMOUNT	PRESSURE	SEDIMENT	CELLS	PERMANGANATE INDEX	GLOBULIN INCREASE	SUGAR	WASSERMANN	LANGE	SPECIAL TESTS
			(Number of c.c. easily removed)			(Number per c. mm. and type)						
Normal	None	Clear	5-10	90 mm. of water in child. 150 mm. in adult	None	1-6 Small lymphocytes	Less than 2	No	0.05-0.1%	Negative	Negative	
Uremia	None	Clear	Normal or Increased	Increased	None	Normal	2 or over	slight or marked	Normal	Negative	Negative	Urea may be increased. Chlorides occasionally increased.
Diabetes	None	Clear	Normal	Normal	None	Normal	2 or over	No	Above 0.1%	Negative	Negative	Acetone may be present.
Skull fracture(without meningeal hemorrhage)	None	Clear	Normal or greatly increased	Normal or Increased	None	Normal	Less than 2	No	Normal	Negative	Negative	
Meningeal hemorrhage (a) bloody	None	Bloody	Increased	Increased	Bloody	Many red and white	Above 2	Yes	Normal	Negative	Negative	Cholesterol present. Serum albumin in large quantities.
(b) clear (Old standing)	None	Clear	Normal or Increased	Increased	None	5-10 small lymphocytes	2 or over	Slight	Normal	Negative	Negative	Cholesterol present. Serum albumin may be present in large quantities.
Lateral sinus Thrombosis	None	Clear	Normal or Increased	Increased	None	Normal	Normal	No	Normal	Negative	Negative	
Brain tumor	None	Clear	10-15	Slightly increased	None	10-15 Small or large lymphocytes	Normal	Slight	Normal	Negative	Occasionally 044230-0000	Inhibition of hemolysis described by Hauptmann. Increased cholesterol.

TABLE XII—CONTINUED.

CEREBROSPINAL FLUID FINDINGS IN VARIOUS CONDITIONS

CONDITION	ORGANISM	COLOR	AMOUNT	PRESSURE	SEDIMENT	CELLS	PERMANGANATE INDEX	GLOBULIN INCREASE	SUGAR	WASSERMANN	LANGE	SPECIAL TESTS
Brain abscess (a) not ruptured	None	Clear	Slightly increased	Slightly increased	None	10-15 Small lymphocytes Occasionally large lymphocytes	Normal	Slight	Normal	Negative	Occasionally 044430-0000	
(b) ruptured	Any organism	Turbid	Increased	Increased	Yes	Several thousand polymorphonuclear leucocytes	Above 2	Marked	Normal	Negative	000000-4444	
Spinal cord tumor	None	Yellow (Xanthochromia)	Decreased	Decreased	Coagulates spontaneously	None or 1-2	Above 2	Marked	Normal	Negative		
Syphilis of central nervous system												
(a) Gen. Paresis	None	Clear	10-40	Increased	None; Occasionally small flocculi	40-200 Small lymphocytes	Normal	Marked	Normal	Positive	555550-0000 (Paretic curve)	
(b) Cerebrospinal syphilis	None	Clear	Increased 15-30	Increased	None	100-20 Small lymphocytes	Normal	Yes	Normal	Positive	005555-0000	
(c) Tabes dorsalis	None	Clear	Increased	Increased	None	60-80 Small lymphocytes	Normal	Yes	Normal	Positive	005550-0000 (Tabetic curve)	

TABLE XII—CONTINUED.

CEREBROSPINAL FLUID FINDINGS IN VARIOUS CONDITIONS

CONDITION	ORGANISM	COLOR	AMOUNT	PRESSURE	SEDIMENT	CELLS	PERMANGANATE INDEX	GLOBULIN INCREASE	SUGAR	WASSERMANN	LANGE	SPECIAL TESTS
(d) Juvenile paresis	None	Clear	Increased	Increased	None	40-80 Small lymphocytes	Normal	Yes	Normal	Positive	555550-0000	
Meningism	None	Clear	Increased	Increased	None	Normal or slightly increased	Normal	No or slight	Normal	Negative	Negative	
Epidemic encephalitis	Minute filterable virus described by some authors	Clear	10-30	Increased	None	10-20 Small mononuclear	Normal	Slight	Normal	Negative	Negative	
Anterior poliomyelitis	Micrococcus described by some authors	Clear	Increased	Increased	None	10-100 polymorphonuclear very early, mononuclear after second day	Normal	Yes	Normal	Negative	Luetic zone early. Meningitic zone later	
Tuberculous meningitis	Tubercle bacilli	Clear or slightly opalescent	Increased	Increased	Fine pellicle	30-400 Mononuclear	Above 2	Yes	Normal or less	Negative	Between luetic and meningitic zones. (000023-3000)	(1) Cataphoresis to the anode. (2) Sulphosalicylic precipitate 3-6 mm. Bichloride of mercury 6-20 mm. (3) Guinea pig inoculation shows tubercles

TABLE XII—CONTINUED.

CEREBROSPINAL FLUID FINDINGS IN VARIOUS CONDITIONS

CONDITION	ORGANISM	COLOR	AMOUNT	PRESSURE	SEDIMENT	CELLS	PERMANGANATE INDEX	GLOBULIN INCREASE	SUGAR	WASSERMANN	LANGE	SPECIAL TESTS
Meningococcus meningitis	Meningococcus	Turbid	Increased	Markedly Increased	Thick, Varying with stage of disease	50-8000; 95% Poly's; Endothelial cells present	Above 3	Marked	Absent or greatly diminished	Negative	Meningitic zone 00000-45555	(1) Cataphoresis to the cathode. (2) Agglutination of bacteria by specific serum. (3) Precipitation of fluid with antimen. serum (4) Sulphosalicylic acid 7-20 mm., Bichloride 5-6 mm.
Pneumococcus meningitis	Pneumococcus	Turbid	Increased	Increased	Present	50-8000 98% Poly's	Above 2	Yes	Normal or diminished	Negative	Meningitic zone	Agglutination. Sulphosalicylic 7-20 mm.; Bichloride 5-6 mm.
Streptococcus meningitis	Streptococcus	Turbid	Increased	Increased	Yes	50-1000 98% Poly's	Above 2	Yes	Normal or diminished	Negative	Meningitic zone	Sulphosalicylic 7-20 mm. Bichloride 5-6 mm.
Influenza meningitis	Influenza bacillus	Turbid	Increased	Increased	Yes	50-1000 98% Poly's Occasionally 50% lymphocytes	Above 2	Yes	Normal or diminished	Negative	Meningitic zone	Sulphosalicylic 7-20 mm. Bichloride 5-6 mm. Indol test described.
Other Meningitis	Specific organism	Turbid	Increased	Increased	Heavy	50-1000 98% Poly's	Above 2	Increased	Normal or diminished	Negative	Meningitic zone	

meningitis, in certain stages of poliomyelitis, the cells are mainly lymphocytes. On the other hand, the cells in all suppurative meningitis are mainly polymorphonuclear in type. In addition to the polymorphonuclear cells, however, there are also endothelial cells. This type of cell is particularly predominant in meningococcus meningitis. The same is true with the phagocytes which are present in large number in meningococcus meningitis. In tumor of the brain large lymphocytes may be present in considerable number. (Fig. 27.)

Method of Counting Cells.—A special counting apparatus has been devised by Fuchs and Rosenthal for the counting of cells in cerebrospinal fluid. This

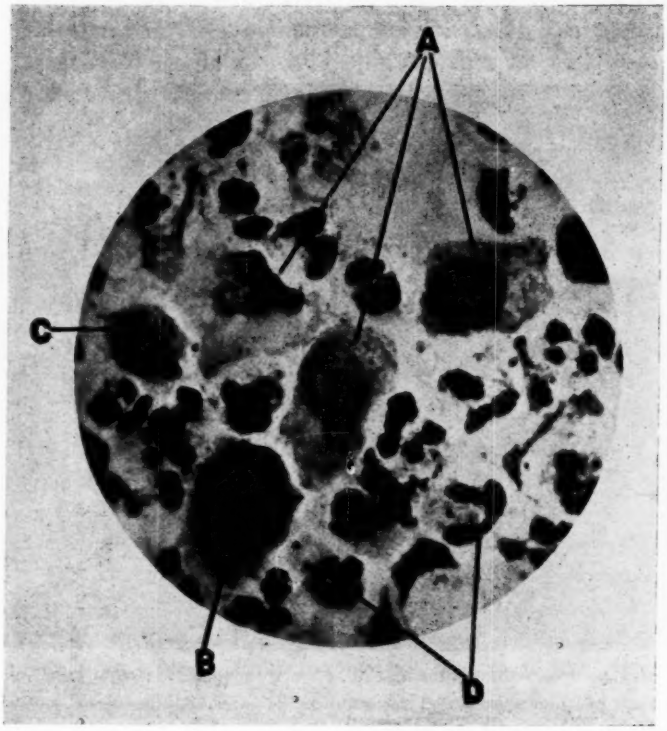

Fig. 27.—Photomicrograph showing types of cells in pathologic cerebrospinal fluid. x1000. *A*, endothelial cells. *B*, endothelial cell which has engulfed a polymorphonuclear leucocyte. *C*, large mononuclear cell. *D*, polymorphonuclear leucocytes.

chamber is 16 mm. square instead of 9 mm. as in the blood counting chamber, and is 0.2 mm. deep instead of 0.1 mm., as in the blood counting chamber. This chamber, therefore, allows of a smaller error than the blood chamber. In using this chamber the cerebrospinal fluid is drawn up to mark 1 in the leucocyte pipette and the diluting fluid to mark 11. The cells in the whole chamber are counted and the resulting number is multiplied by 11 and divided by 32. As a diluent for the fluid, a solution of methyl violet (methyl violet 0.2 gm. glacial acetic 5 c.c. and water to 100 c.c.) has been found very useful, although ordinary 2 to 3 per cent acetic acid will do to destroy the red cells in the fluid. The Fuchs-Rosenthal chamber, while more accurate,

is not absolutely necessary, an ordinary blood counting chamber will suffice. The technic is as follows:

The methyl violet or other diluent is drawn up to mark 1 in the pipette and the cerebrospinal fluid to mark 11. In order to obtain the number of cells in one cubic millimeter of undiluted fluid, the result obtained is multiplied by 11 and divided by 9. A rougher yet fairly accurate clinical method is to draw up glacial acetic acid in the pipette and blow it out, and then draw up the cerebrospinal fluid. This is sufficient to dissolve the red blood cells. No allowance has to be made, then, for diluting fluid. The cells must be counted immediately after withdrawal from the body, as they undergo autolysis on standing. If it is impossible to count cells in the fluid immediately after its withdrawal from the body, the cells may be preserved by the addition of 2 to 3 drops of a 3 per cent acetic acid solution to 5 c.c. of

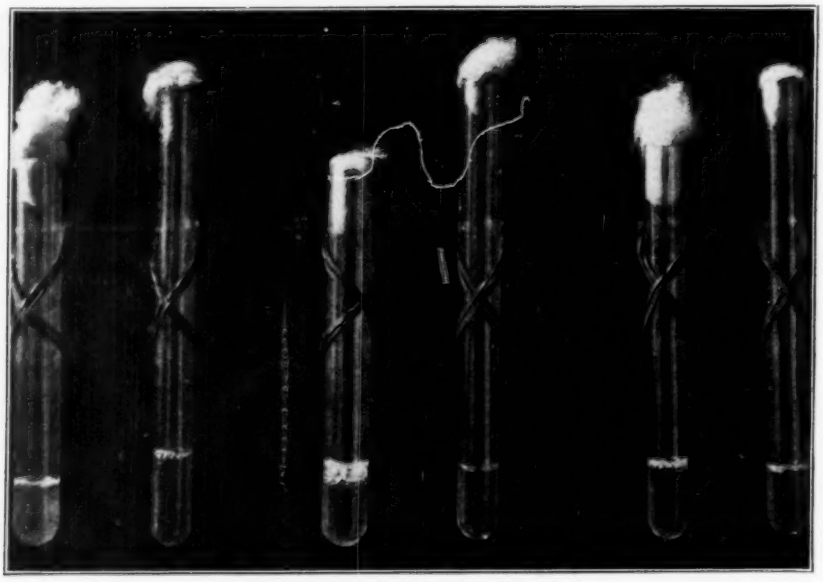

Fig. 28.—Photograph showing agglutination of meningococci by the macroscopic method.

A. Emulsion of meningococci + 1:10 dilution of antimeningococcus serum.
B. Control of emulsion of meningococci + salt solution.
C. Emulsion of meningococci + 1:160 dilution of antimeningococcus serum.
D. Control.
E. Emulsion of meningococci + 1:640 dilution of antimeningococcus serum.
F. Control.

cerebrospinal fluid. The subsequent count will not be very accurate, but will give a good idea of the number of cells in the fluid.

Differential Cell Count.—When the fluid is turbid as in suppurative meningitis, a differential cell count may be made on an uncentrifuged fluid. If the fluid is clear or only slightly opalescent, it is best to centrifuge the fluid for from fifteen to thirty minutes at about 1500 revolutions per minute. It should be stained with Wright's stain or methylene blue.

Bacteriological Examination.—In suppurative meningitis where the cerebrospinal fluid is thick, a slide may be prepared from the uncentrifuged fluid. When the fluid is clear, it should be centrifuged for several minutes,

and the sediment examined. Where suppurative organisms are suspected, it is best to stain with both methyl blue and Gram stain. When tubercle bacilli are searched for, the fluid should be allowed to centrifuge at high speed for thirty to sixty minutes and stained by the Ziehl-Neelsen method. If a pellicle is found in the fluid, the pellicle should be stained for tubercle bacilli.

CULTURE MEDIA.—Several drops to 1 c.c. of cerebrospinal fluid or its sediment are planted on a culture media, the kind of media depending on the bacteria looked for. In cases suspicious of poliomyelitis anaerobic cultures should be made, as it is claimed that in this way the organism will be found in culture. In most other cases blood agar is the best culture medium. The culture is examined after 24 and 48 hours incubation.

Agglutination.—In order to make certain that the antimeningococcus serum used in treating a given case of meningococcus meningitis is specific for

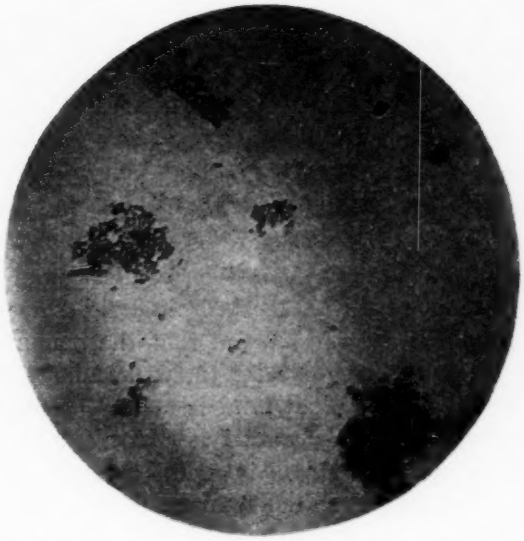

Fig. 29.—Agglutination of meningococci by the microscopic method. (Magnification 800 diameters.)

the particular strain of meningococcus in question, the bacteria obtained by culturing the cerebrospnal fluid of the patient should be tested by the antimeningococcus serum used for treatment. Unless the bacteria are agglutinated by the serum, the given serum is not to be used in the treatment, and a serum must be found that will agglutinate the particular strain of meningococcus in question.

Technic.—Two methods have been described for this purpose: the macroscopic and the microscopic.

The macroscopic method is carried out by washing down the growth of the culture in question with two or three c.c. of an 0.8 per cent sterile salt solution, and adding 0.2 c.c. of this emulsion to various dilutions, (1:10, 1:20, 1:40, etc., to 1:2000) of antimeningococcus serum, and incubating it for 15 to 20 hours. If the bacteria in the culture is meningococcus, a floccu-

lent precipitate will appear in the tubes, containing as high a dilution as 1:2000, or even higher. If it is not meningococcus, it will either not agglutinate at all, or it will agglutinate only in very low dilutions, such as 1:50, or 1:10.

The microscopic method consists of using one drop of antimeningococcus serum, one drop of whole human blood in a sodium citrate solution (1 drop of blood to 2 per cent sodium citrate in salt solution), and one drop of a suspension of the organism to be tested. This is mixed in a pipette, heated for 20 minutes, spread on a slide, stained and examined under the microscope. If the bacterium is meningococcus, a distinct clumping will be seen under the microscope. This should be controlled by a suspension of meningococcus with normal horse serum, or by a suspension of some other bacteria with antimeningococcus serum. (Figs. 28 and 29.)

Guinea Pig Inoculation.—Five to 10 c.c. of cerebrospinal fluid is injected subcutaneously into the anterior abdominal wall of a normal guinea pig. The needle should be pointed downward and laterally toward the inguinal region. Six weeks later, or sooner in case the guinea pig dies, an autopsy should be performed and the inguinal and mesenteric lymph nodes, as well as the liver and spleen, should be examined for tubercles.

WASSERMANN REACTION.—While there are diseases other than syphilis, such as leprosy or sleeping sickness, that give a positive Wassermann reaction, the test is sufficiently reliable to consider the patient syphilitic when the reaction is positive.

The technic of the Wassermann test on cerebrospinal fluid is the same as that on blood, except that the cerebrospinal fluid does not have to be heated as in the case of blood serum; and that the amount of cerebrospinal fluid taken for each test must be greater than the amount of blood used.

Usually 0.2 c.c. of cerebrospinal fluid is taken for each of the tubes set up, varying the amount of antigen added to the tubes. As a control 0.4 c.c. of cerebrospinal fluid without antigen is used. Schottmuller advises the use of different amounts of cerebrospinal fluid in each of the test tubes. This gives a more or less quantitative result as to the degree of positiveness of the fluid.

(To be continued.)

THE EFFECT OF BUFFER SALTS ON BLOOD COAGULATION*

By Benjamin Jablons, M.D., New York City

FOR a long time it has been known that certain salts have the property of retarding coagulation of blood when added to blood in vitro. Some of the more commonly known salts employed for this purpose are the citrate, fluoride and oxalate of either sodium or potassium. The oxalate is supposed to act by virtue of its ability to precipitate the calcium in an insoluble form. This is similarly true of the fluoride. Citrate, on the other hand, although its action is not completely understood, is supposed to produce its anti-coagulating effect through its dispersion of the calcium ion. The effect of buffer salts on the clotting of blood has not been studied, as far as can be gathered from a perusal of the available literature. Some recent experiments carried out on the physical and chemical changes involved in the clotting of blood would indicate that hydrogen-ion concentration plays an important rôle in this process. It was, therefore, thought advisable to study the effect of the addition of various buffer salts on feshly drawn blood, and to compare this effect with the addition of other salts.

To a series of tubes containing respectively sodium chloride, sodium citrate, sodium bicarbonate, sodium taurocholate, monobasic and dibasic potassium phosphate, freshly drawn human blood was added in 1 c.c. amounts. The clotting time was controlled by the addition of 1 c.c. of blood to a clean tube in which no salt had been placed. The effect on the blood can be seen from the appended tables. Blood No. 2 represents a specimen taken from a patient suffering from thromboangiitis obliterans; blood No. 1, from a normal subject. One noticeable feature about the reaction was the varied effect of the various salts on blood coagulation. In the first experiment sodium bicarbonate had been omitted. The blood was allowed to remain at room temperature, so that any possible hemolytic effect might be noticed in the supernatant plasma or serum, after the clot or cells had settled to the bottom of the tube. A striking phenomenon noticed was the inhibition of coagulation produced by the buffer salts. The effect was similar to that which was obtained with sodium citrate. Both of these bloods clotted normally within three minutes after being drawn. In the first instance, the blood drawn from the thromboangiitic patient clotted after ten minutes when added to sodium chloride. This phenomenon also occurred in the tube to which sodium taurocholate had been added. No hemolysis was evident in the control tubes containing the normal blood and blood taken from the thromboangiitis case. The tubes containing sodium chloride in both instances showed hemolysis. The taurocholate tubes in both instances showed very marked hemolysis with production of a soft clot. The tubes containing

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sodium bicarbonate similarly showed marked hemolysis, although the clot failed to show the presence of methemoglobin after twenty-four hours. The tubes containing sodium citrate, while remaining incoagulable, showed definite hemolysis in the supernatant plasma. The tubes to which the buffer salts had been added showed a very interesting phenomenon. In the tubes containing the dibasic potassium phosphate, the blood remained incoagulable for forty-eight hours, and the blood was bright red in color resembling arterial blood or blood containing oxy-hemoglobin. This was evident in both

TABLE I

	2½ MIN.	5 MIN.	7½ MIN.	10 MIN. OVER
Control containing blood alone 1 c.c.*	±	++	++	++ No change
Sod. Citrate 0.1 gm. Blood 1 c.c.	0	0	0	0
Sod. Chloride 0.1 gm. Blood 1 c.c.	0	++	++	++
Dibasic Pot. Phosphate 0.1 gm. Blood 1 c.c.	0	0	0	0
Monobasic Pot. Phosphate 0.1 gr. Blood 1 c.c.	0	±(soft clot)	+(soft clot)	+(soft clot)
Sodium Bicarbonate 0.1 gr. Blood 1 c.c.	++(3 min.)	(+) (soft clot)	+(soft clot)	+(soft clot)

*Blood taken from normal patient.

TABLE II

	2½ MIN.	5 MIN.	7½ MIN.	10 MIN.	12½ MIN.	15 MIN.	20 MIN.
Control containing blood alone 1 c.c.*		(coag 5 min.) +	+	+	+	+	+
Sod. Citrate 0.1 gm. Blood 1 c.c.	0	0	0	0	0	0	0
Sod. Taurocholate Blood 1 c.c. 0.1 gm.	0 (thick)	±	+	++	++	++	+
Monobasic Pot. Phosphate 0.1 gm. Blood 1 c.c.	0	0	0	0	0	0	0
Dibasic Pot. Phosphate 0.1 gm. Blood 1 c.c.	0	0	0	0	0	0	0
Sod. Chloride 0.1 gm. Blood 1 c.c.	0	±	+(?)	+(?)	++	++	++

*(Blood taken fifteen minutes after intravenous injection of buffered citrate solution.)

the normal and pathologic blood. In the tube containing the monobasic phosphate, on the other hand, the blood, while apparently remaining incoagulable, became very dark in a very short period of time as compared with the tube to which the dibasic phosphate had been added. The viscosity of the blood to which monobasic potassium phosphate had been added, seemed similarly increased, the blood failing to flow as freely as in the tube containing the dibasic potassium phosphate. The change in color was very striking, the blood after twenty-four hours having a chocolate hue, whereas the dibasic

phosphated blood had even a lighter hue than when originally drawn (blood was taken from median basilic vein). Hemolysis was only slightly present in the dibasic phosphated blood, whereas it was much more marked in the blood containing the monobasic phosphate.

One sample of blood which had been kept and which was prevented from coagulating by the addition of the buffered citrate solution (sodium citrate, sodium chloride, and buffer salts) failed to show any hemolysis after forty-eight hours.

FAMILIAL HYPERTENSION WITH REPORT OF A CASE*

By Jacob Rosenbloom, M.D., Ph.D., Pittsburgh, Pa.

I. INTRODUCTION

WHILE it is true that today we know there are certain diseases that are hereditary, it is not generally known that there exists an hereditary type of hypertension.

An explanation[1] of this condition may be offered, if we can accept the "growing point" theory which holds that there are two primary axial points in the early formation of an organism, i.e., positions from which cells and daughter cells extend and developing from these central axial points are formed other secondary or lateral forming points that produce the anlages of the limbs and internal organs.[2] This theory is accepted by biologists to hold for plants and lower organisms and probably a similar primary condition is present in the higher animals with axial growing points in the pituitary region (superior) and sacral region (inferior) from which lateral growing points extend to reproduce the limbs and internal organs. The pattern of these growing points for the different species is undoubtedly inherited. Abnormalities form from a splitting or cleavage in a growing point and when it is an axial point, there is produced the teratoid monster with duplicate heads and trunks, etc., and when it is one of these secondary growing points there are produced limbs or organs. We know that many of these results of abnormal cleavage are called mutations and are inherited according to Mendelian ratios, for example, polydactylism.

In the plant, the primary growing points are active throughout its existence, whereas in animals they cease to function as such when the anlages of the brain and the nervous system have been developed; if for some reason they do not cease to function, the tissue is forced through the roof of the mouth forming a teratoma, or if the inferior, a sacral teratoma is produced.

If the secondary growing points escape abnormal cleavage, thus producing duplicate organs (and they of course usually do escape), they develop the anlage of the limbs and organs, which vary in size according to the

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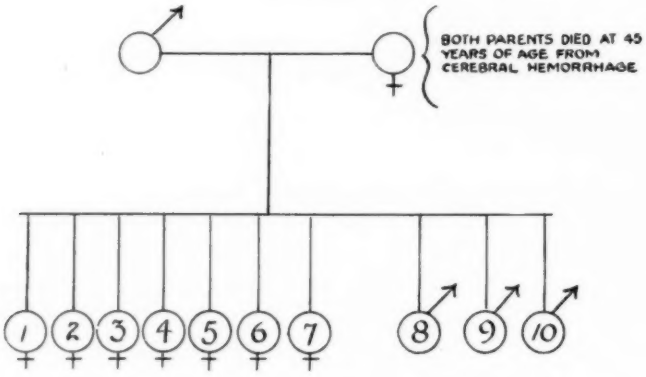
amount of original "vital" or chemical energy released and evidently an organ cannot develop beyond the original possibilities of the anlagen which explains the state termed aplasia or arrest in development, which, after all, is not an arrest in but the extent of development, that is the organ is normal in shape and fully developed according to its possibilities, but with its functional capacity lowered in keeping with the size. Certainly there is proof enough from biological investigation that cellular potentialities are inherited, for this one need go no farther than Morgan's studies on heredity in the fruit fly (Drosophila Amphylopla).

I think that the hereditary factors in the case of family hypertension that I am describing, lie somewhere in the potentialities of these secondary growing points.

II. DESCRIPTION OF CASE

Following is the family tree of case of familial hypertension:



Let us now consider these descendents separately:

1. Died at forty-seven years from cerebral hemorrhage. Had suffered from hypertension.

2. Is forty years and has hypertension.

3. Is forty-four years old and has hypertension.

4. Is forty-six years old. Systolic 290, diastolic 140.

5. Is forty-nine years old. Systolic 220, diastolic 160.

6. Is thirty-five years old. Blood pressure normal. Will she develop hypertension between the ages of forty to forty-five years?

7. Is thirty-three years old. Blood pressure normal. Will she develop hypertension between the ages of forty to forty-five years?

8. Died at forty-seven years. Had hypertension. Systolic 240, diastolic 160.

9. Died at forty-five years of age. Had hypertension.

10. Died at forty-two years of age. Had hypertension. Systolic 240, diastolic 140.

Case four was married to person who died at fifty years of age and who suffered from high blood pressure for ten years previous. They have a

daughter aged twenty under my care who is normal except for constipation. Will she develop hypertension between the ages of forty to forty-five years?

Raymond[3] cites some cases which showed a family fate as regards a disposition to hypertension and cerebral hemorrhage. Albutt[4] states that in respect to arteriosclerosis there are two modes of hereditary transmission, the direct and the indirect; the direct, that form which he has named the decrescent, or primary, which consists apparently either in an original frailty or toxic suspectibility of the arterial structure, a frailty or susceptibility which like other such peculiarities, may run in families; the indirect, that form which he has named the hyperpietic, a secondary event, which apparently depends not upon an original arterial frailty but upon a proclivity to some ill-understood poisoning or perversion making for high blood pressures; and to these high blood pressures it is that the soundest arterial structures, thus subjected to praeternatural stresses will succumb. He also emphasizes the fact that we must separate high blood pressure cases from premature arterial decay.

Ehrmann[5] has lately described a case of familial arteriosclerosis, extending for two generations.

Of the cases that I describe, Cases 4, 5, and 10 have been under my observation for some years, a Jewish family, very active, successful, and of a nervous temperament. They first present symptoms of hypertension but most of the tests for kidney function are normal. After several years the kidney function tests show kidney involvement, and casts and occasional protein is present in the urine. These cases seem to bear out the ideas of Moschcowitz,[6] Albutt, and others, who consider the hypertension a primary disease and the nephritis secondary.

It is certainly true that no one can view the family tree given in this paper without feeling that heredity has produced in this group either a congenital aplasia of the arterial system, or a susceptibility to some endogenous toxic substance whose effect shows itself between the ages of forty to forty-five years.

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LABORATORY METHODS

A PORTABLE IRRIGATION APPARATUS FOR THE TREATMENT OF WOUNDS WITH LIQUID ANTISEPTICS*

By Beverly Douglas, M.D.

ABOUT 24 months ago the writer began a study of wound irrigation with a view of improving methods. Individual open bowls with small hand syringes as commonly used for irrigation seemed to offer many disadvantages from waste of solution by spilling and evaporation and from danger of contamination. From the nurse's standpoint they were not convenient. Individual closed gravity irrigators seemed to involve unnecessary expense both from the high initial cost and from breakage and rubber deterioration.

The portable irrigator herewith described is the result of experiments to simplify and standardize the diverse forms of apparatus employed for the treatment of wounds with antiseptic solutions. We regard it as an improvement over the apparatus of le médecin-major Perret described for war use by Carrell and Dehelly† and consisting of a reservoir of Dakin's solution supported at the proper height on a dressing wagon. The experimental and practical work with it was done with the co-operation and aid of the surgical and nursing staffs of the Johns Hopkins and of the New Haven Hospitals whose valuable assistance is gratefully acknowledged.

DESCRIPTION

On account of limits of space we are unable to give more than an outline of construction here. As put upon the ward it is arranged as shown in the drawing.

The *Carrier* has a circular base (1) of rigid lacquered metal with an aluminum deck (2) provided with four circular perforations of sizes to fit the two bottles and two sterile-tip containers. Attached to one of the upright portions of the handle (4) is a pair of adjustable hooks by means of which the apparatus can be suspended from the bed or carriage. The larger container is preferably an opaque bottle of half-gallon capacity which serves as a reservoir. The rubber stopper for it is held in place by a wire strap (7) secured to a metal collar. The smaller container is provided with a gage consisting of a vertically extending series of graduations (16); each graduation preferably indicating an ounce of solution. It is transparent so that the amount delivered from the large container can be

*From the Department of Surgery, Yale University.
Received for publication, March 2, 1923.
†"Infected Wounds"—Carrell and Dehelly, 1917, New York, Paul B. Hoeber Co.

readily determined. The stopper of the larger bottle is secured by a collar and a strap.

It is hardly necessary to go into details of the disposition of the glass and rubber tubing, and the bulb and tip, except to say at (17) a horizontally disposed "L" tip is connected by a small rubber tube to the lower end of the gaging pipe. This tip is flattened at its distal portion so that its aperture may be accurately positioned by raising or lowering the gage pipe (15). Attached to the outer end (15) is a rubber tube of sufficient length to reach conveniently from the head of the bed to the feet of the patient. When not in use it is kept wound upon the reel as shown. Near its end is a small snap thumb clamp (11) with which the discharge of solution may be regulated. Sterile glass dropper tips are provided in one of the small tip

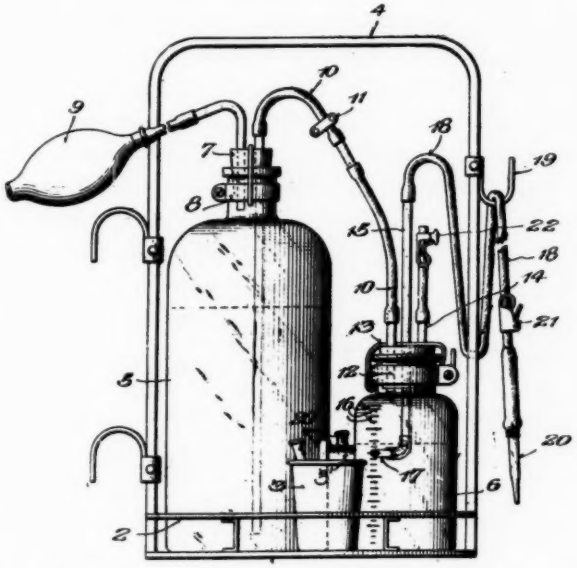


Fig. 1.—A portable irrigation apparatus of extensive application in wound treatment with antiseptic solutions.

containers (3). These are changed after each dressing and the used tip placed in the other small tip container (3)′.

METHODS OF IRRIGATION

In operation the large container is filled with Dakin's solution, bichloride or other antiseptic, the clamp between the two bottles is opened and by pressure created in the first bottle by the hand bulb the liquid is forced to flow into the smaller graduated container until the latter is filled to the uppermost graduation. The apparatus is then ready for use either for (1-A) forced feed irrigation, *without measurement* (1-B) forced feed irrigation *with* measurements or for (2) *a gentle siphon feed irrigation.* To accomplish (1-A) the vent pipe (14) is closed by a stopcock and the tip (17) on the lower end of the gage pipe (15) is positioned immediately below the level of the liquid in the small container, then by pressing the bulb, liquid is forced from the

large to the small bottle and from the latter through the gage pipe and tubing (18) to leave through the sterile tip. The level in the container remains constant as long as any solution is left in the large bottle. To accomplish (1-B) the hand bulb (9) is removed from the first bottle and connected with the smaller one through the vent pipe (14) and the screw clamp (11) between the two bottles is closed so as to prevent back flow of solution from the latter to the former. The gage pipe is then lowered to any point desired below the level of the liquid depending on the exact quantity which the operator wishes to inject. This method allows any amount of solution to be expelled from the sterile tip under any desired pressure from the hand bulb. To accomplish (2) the siphonic feed irrigation, which is the usual method employed on the wards, the graduated container is filled as described and the lower end of the gage pipe (15) is positioned at any point on the graduation depending on the amount of solution to be used for particular irrigation. The vent pipe (14) is then opened and the tray suspended above the patient preferably on the bed by means of the hooks. The only precaution necessary is to have the graduated container above the level of the dropper tip when the latter is in position to irrigate the wound. With the apparatus in this position the solution will be discharged from the container by siphonic action until the liquid in it drops below the lower end of the gage pipe. *The bubbles of air which will then rise in the gage pipe (15) will indicate to the operator or attendant that the desired amount of solution has been discharged* so that he may instantly shut off the clamp at the end of the tube and may stop the flow of solution before the action of the siphon *is destroyed by the ingress of air.* Successive irrigations may be accomplished by any one of the three methods by simply changing the glass tip at the end of the outlet tube. Used tips are placed in antiseptic solution in one of the containers. The lightness and portability of the apparatus will be found to facilitate the rapid and sterile handling of the antiseptics during successive irrigations.

ADVANTAGES IN USE

1. It offers a closed system and therefore provides against waste, contamination, and deterioration of solution.

2. The combination of a large dark bottle and a similar transparent gage bottle offers a method of preserving a quantity of chemically unstable solution, while at the same time it provides a ready means for measuring and delivering any quantity at any time. This exactness of delivery has been found very economical.

3. The bubble method of visibly gaging the amount of solution delivered is extremely simple and accurate.

4. The use of sterile tips which may be changed easily from patient to patient saves a large quantity of apparatus and does not hazard the sterility of the wound in the least degree.

5. The use of force feed or siphon feed irrigation at will, and the ability to shift instantly from the one to the other has made its application very

extensive for (A) routine ward irrigation by the Carrell-Dakin technic or (B) for Dakin's bichloride, boric or other moist compresses; (C) for cleansing purposes. The operator has found the apparatus very valuable for cleansing exudate from the surface of grafts or of infected wounds. A particularly useful feature of the force feed method is the fact that where a wound occurs on the lower surface of an extremity or of the trunk it may easily be cleaned by a fine stream of the solution under pressure without touching it with gauze.

SUMMARY

1. The apparatus employed for the irrigation of wounds with antiseptic solutions in the average hospital is needlessly wasteful and inconvenient, and in certain instances insanitary.

2. The apparatus described obviates these disadvantages and standardizes irrigation treatment. This has been demonstrated in the Johns Hopkins and the New Haven Hospitals.

A SIMPLE AIR INTERRUPTER*

By Raymond F. Hacking, Richmond, Va.

THERE are a number of interrupters available for use in carrying out artificial respiration on animals in laboratories equipped with means for compressing air, but, in our experience, these have been quite expensive or unsatisfactory in operation. In order to obtain efficient air interruption at a minimum of expense, the following simple apparatus was constructed out of odds and ends in the laboratory.

Briefly, the apparatus consists of a magnet (obtained from an old Harvard Apparatus Co. Vibrating Interrupter) so placed in regard to a lever that the latter may be caused to open and close an automobile pet-cock. The current for the magnet may be derived from four dry cells or, by means of a transformer, from the ordinary alternating lighting current. To make and break the current, a Harvard kymograph and the spring from the Harvard Vibrating Interrupter have been utilized. The drum of the kymograph is covered with paper in the usual manner; and through the paper, small holes are cut at spaces depending on the rate of the drum's revolution and the number of interruptions desired per minute. The magnet is so wired that the current passes through it when the wire tip of the vibrating interrupter spring comes in contact with the exposed metal of the drum; the current being broken when the revolution of the drum causes the paper to be interposed between the wire tip and the drum. It is essential, of course, that the drum's surface be brightly polished, in order to insure good contact. The current being broken, a spring, obtained from a discarded glass syringe,

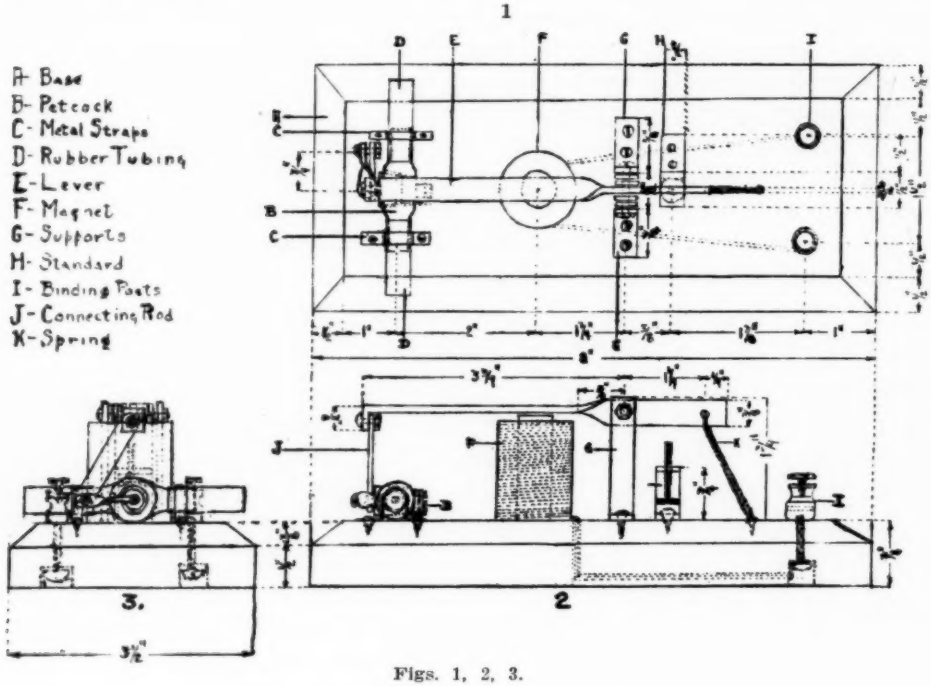
*From the Laboratory of Pharmacology, Medical College of Virginia, Richmond, Va. Received for publication, March 28, 1923.

attached to the end of the lever, draws this end down, thereby closing the valve.

Details of the construction of the apparatus are given in the diagrams, 1, 2, 3; the first giving the appearance as seen from above; the second as seen laterally; while the third shows it as looked at from the end.

The base, A, is a piece of hard wood, 8 x 3½ x ⅞ inches, the edges being leveled. Holes were bored 1 inch from the edge (I) and counter-sunk from the back for the binding screws.

The lever (E) was made from a piece of soft flat steel. Its dimensions were 5⅝ inches long; ⅜ inch wide and; 1/16 inch thick. Three holes, ⅛ inch in diameter, were bored through it;—¼ inch from one end; 1¼ inch from



Figs. 1, 2, 3.

the first hole; and 3/16 from the opposite end. Next, the end of the lever containing the two closely placed holes was placed for two inches of its length between the jaws of a vice, and, by means of a wrench, the remainder of the lever was twisted at right angles to the part in the vice. Finally, ⅜ inch of the longer end of the lever was bent at a right angle.

G, G represent two supports, made from soft steel similar to that used for the lever (⅜ x 1/16). The length of each is 2½ inches, ¾ inch of each being bent at right angles and drilled to receive small wood screws. A hole was drilled ¼ inch from the longer end; and a second hole in the center; these holes being ⅛ inch in diameter.

The standard (H) was made from similar steel and is 1¾ inches long. One-half inch at each end was bent at right angles, the directions being opposite. Two holes were bored in one of the bent pieces, in order that

it would serve at the base while one hole was bored in the other bent end, this hole being tapped to receive a long machine screw.

A connecting rod (J) was made from steel similar to that used in the other metal parts. The length of this rod depends on the type of valve selected. This rod serves the purpose of connecting the end of the lever (E) with the valve stem.

The valve (B) is an automobile pet-cock. It is essential that it work with little friction; to ensure this, the spring was removed and suitable metal washers substituted. The arm of the valve stem was turned at right angles and a hole, $\frac{1}{8}$ inch in diameter was bored $\frac{3}{4}$ inches from the center.

The metal straps (C, C) were made from thin sheet iron, bent to conform to the shape of the valve.

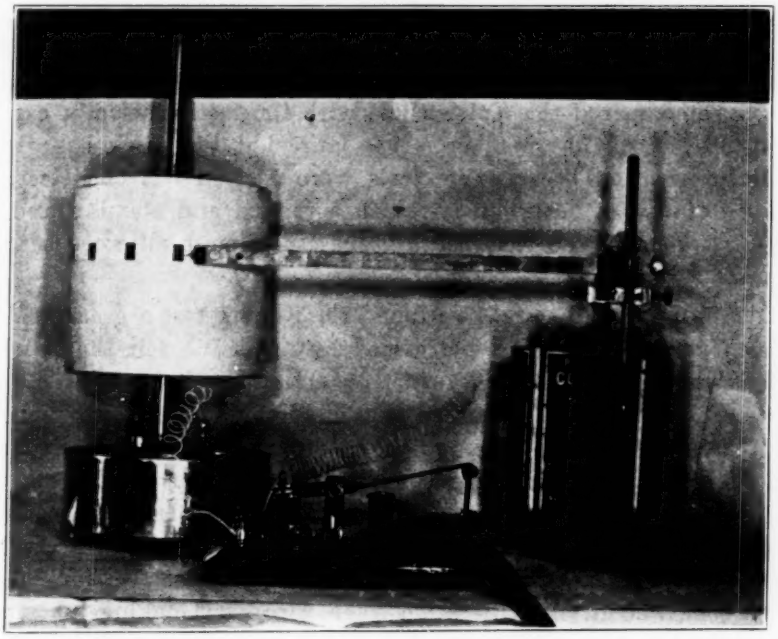


Fig. 4.

The magnet (F) is placed in position, and holes bored through the wooden base to allow the wires to pass to the binding posts (I, I).

Small machine screws were used to connect the valve stem and connecting rod and lever and connecting rod. A long machine screw served as shaft for the lever. The lever was centered between its supports by thin metal washers. The various bearings should be tight enough to eliminate last motion as much as possible but not cause friction too great for the magnet or the light spring to overcome. To prevent or lessen air leakage, it is desirable to lubricate the valve with a heavy oil. A fairly powerful magnet is necessary; the one obtained from the Harvard Vibrating Interrupter was found very satisfactory. It should not be more than $1\frac{1}{2}$ inches high.

The photograph represents the apparatus as set up for use; dry cells being used as the source of the current. Should it be desirable, several rows of holes may be cut in the paper; by this and using a heavily weighted fan, almost any respiratory rate can be obtained; while the relation between inspiration and expiration can be determined by the relative size of the holes and of the intervening paper. It is, of course, immaterial which opening of the pet-cock be used for intake or outlet of the air (D, D).

THE STANDARD WASSERMANN REACTION*

By Reuben Ottenberg, M.D., and Ida Wisler, New York

THE standard Wassermann technic proposed by Kolmer† as the result of a long series of careful studies deserves thorough trial.

We have compared the Kolmer test with the test as usually carried out by us in 204 cases. The number is not large but the work has given considerable information because the tests were carried out on selected cases belonging exactly to the group in which a refined and standardized technic is necessary—namely the weak positive cases;—almost all were cases under treatment.‡

In the first 62 cases tested, we found the Kolmer test a great deal weaker than the Wassermann test as performed by us.§ We felt that perhaps we were not carrying out the test exactly as Kolmer desired. We therefore went to Dr. Kolmer's Laboratories in Philadelphia where we picked up a number of finer points of technic which are worth describing. Thus we learned that sodium chloride in the form of tablets for normal salt solution (Parke, Davis & Co.) was not satisfactory. It interfered to some extent with hemolysis (probably due to other substances than NaCl present in the tablet). Merk's C.P. NaCl was better. We found that we had been using too much complement. In a titration where two hazy looking tubes preceded a tube that was completely hemolyzed, one could safely choose as "one full unit," the tube directly before the completely hemolyzed one. We were told that one could take final readings on the daily titrations at the end of 40 to 45 minutes instead of waiting the full hour.

Also, in comparison to the 2 per cent cell emulsion used in Kolmer's laboratory, the 2 per cent cell emulsion that we had been using was distinctly

*Received for publication, March 22, 1923.

†Kolmer, The Jour. of the Am. Med. Assn., Sept. 3, 1921, lxxvii, 776-778. Also series of thirty-two papers published beginning in the Am. Jour. of Syph., Jan. 1, 1919.

‡We are indebted for many of the cases obtained from the Vanderbilt Clinic to Dr. J. G. Hopkins.
We are indebted to Dr. Kolmer for the antigen used.

§Ottenberg, Methods of Determining the Optimal Amount of "Antigen" for the Wassermann Reaction. Journal of Immunology, ii, No. 1, Dec., 1916.
Correct and Incorrect Methods of Performing the "Daily Titrations" for the Wassermann Reaction and Other Forms of Complement Fixation. Journal of Immunology, ii, No. 1, Dec., 1916.
On the Reliability of the Wassermann Reaction, Archives of Internal Medicine, March, 1917.

weaker. Therefore, when we again took up the work we always at the last washing of our sheep cells, centrifuged for 25 minutes instead of 10 minutes in order to get the same concentration of cells as Dr. Kolmer was using.

It was about this time also that Dr. Kolmer announced the fact that he was changing his dosage of patient's serum by decreasing his amounts more gradually.

All these points we applied to the remaining 142 cases that were tested out. These yielded much more satisfactory results, and on these cases we shall report.

Our average complement titre agreed very well with that of Dr. Kolmer. We tried the use of 1, and 1½ units of complement along with the regular 2 full units of complement prescribed by Kolmer. While better fixation was obtained in many instances, more or less anticomplementary effects resulted in others. We therefore adhered to the use of 2 full units of complement throughout. The quantities of the ingredients for the Kolmer test correspond to half the quantities of the original Wassermann test in a total volume of 3.0 c.c., and the sheep cells are a 2 per cent emulsion.

Each Kolmer test was checked up by a Wassermann test using alcoholic antigen, and 4 hours ice box incubation, and by a Wassermann test using cholesterinated antigen and 1 hour at 38° C. incubation. Both tests were the Citron modification used by us as a routine for the last seven years.

The following are the results:

TABLE I

NUMBER OF CASES	KIND OF CASES	KOLMER'S RESULTS	R. O. ALC.	RESULTS CHOLEST.	REMARKS
123	Known syphilis	+++ or ++++	+++ or ++++	+++ or ++++	Agreement excellent
5	Negative	neg.	neg.	+ or ++	Agreement excellent
1	Treated case	+++	neg.	neg.	Kolmer's test detected 1 case
1	Inherited syphilis No symptoms	neg.	neg.	+++	This same result obtained on three different occasions with this patient.
12*	Treated cases	neg.	+ to ++++	+ to ++++	*Seven out of these 12 cases Kolmer missed entirely due to presence of natural amboceptor.
142					

CONCLUSIONS

The Kolmer test is a good test and might safely be adopted as a standard. There was excellent agreement in the majority of 142 cases.

ON THE OTHER HAND

The Kolmer test is a rather elaborate two-day test. It uses up much more materials than the Wassermann test. We did not find the Kolmer test more sensitive or reliable than the Wassermann test carefully done according to the technic adopted by us seven years ago. There was a small but definite number (12 cases, 8 per cent) of treated cases which the Kolmer test did not detect at all—cases ranging from doubtful to strongly positive. In many instances this was due to disregard of natural antisheep amboceptor.

On the whole we believe that Kolmer's work offers the best basis yet proposed for a standard technic, but it will have to be somewhat shortened and some way will have to be introduced for dealing with natural antisheep hemolysin.

THE KOTTMANN REACTION FOR THYROID ACTIVITY. CARBON DIOXIDE IN THE TESTED SERUM*

By Sterne Morse, M.D., and Clyde M. Fitch, M.D., Columbus, Ohio

SINCE the original publications by Kottmann,[1-2] in 1920 and the appearance of several articles in this country by Petersen, H'Doubler, Levinson and Laibe in 1922,[3-4] considerable interest has been aroused concerning the possibilities of the Kottmann Reaction. In these papers the chief interest has centered around clinical results, which have been very gratifying to these workers. One of the main problems in the work, so far, has been to determine just what relation this reaction may or may not bear to thyrotoxicosis. To date we have performed over 195 Kottmann reactions on known and suspected cases of goitre.

The technic employed is the same as that employed by the originator[1] of the reaction. The principle is based on a well-known phenomenon observed in photography. When silver nitrate is added to potassium bromide a precipitate of silver bromide is formed and if a colloid such as gelatin is present this suspension is so fine as to be colloidal. The photochemical activity of this colloidal silver bromide seems to depend upon the size of the particles of silver bromide in the gelatin. After the gelatin plate or film is allowed to ripen the colloidal particles become larger and also more photosensitive. When a protective colloid is present the coagulation of the silver bromide particles is retarded, and the emulsion consequently remains less photosensitive. In the Kottmann Reaction, serum is substituted for the gelatin and silver iodide for silver bromide, and it is supposed that a silver iodide suspension takes place in the patient's serum. The rapidity of the reaction is supposed to depend upon the amount of protective power of the serum being used in each test.

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*From the Laboratory of Grant Hospital, Columbus, Ohio.
Read before the Columbus Academy of Medicine, November 27, 1922.
Received for publication, March 12, 1923.

The test is performed in a dark room with a red light for illumination. To 1 c.c. of the patient's serum (freshly drawn) is added 0.25 c.c. of a 0.5 per cent solution of potassium iodide and 0.3 c.c. of a 0.5 per cent solution of silver nitrate, thus making a silver iodide suspension in the serum. Reagents in the reaction are prepared fresh and measured accurately. After a slight shaking to insure thorough mixing the serum is exposed for five minutes to

TABLE I

11-17-22	2½ MIN.	5 MIN.	10 MIN.	15 MIN.	20 MIN.	30 MIN.	40 MIN.	1 HOUR
Mrs. T.—								
Nonaerated	O	O	F	L	L	L	L	Incomplete
Aerated 15 min.	F	L	L	L	L	L	L	Incomplete
Mrs. P.—								
Nonaerated	O	O	O	F	L	L	Unchanged	
Aerated blowing with mouth	O	O	F	F	F	F	L	Incomplete
Mrs. D-*-*-V—								
Nonaerated	O	F	L	L	L	L	D	
Aerated 10 min.	L	D	D	D	D	D	D	
Mrs. P.—								
Nonaerated	O	O	O	F	L	L	Incomplete	
Aerated 5 min.	O	F	F	L	L	L	Incomplete	

TABLE II

11-18-22	2½ MIN.	5 MIN.	10 MIN.	15 MIN.	20 MIN.	30 MIN.	40 MIN.	1 HOUR
Mrs. W.—								
Nonaerated	O	F	L	D	D	D	D	
Shaken violent	F	L	D	D	D	D	D	
Aerated 5 min.	O	F	F	F	F	L	L	
10 min.	L	D	D	D	D	D	D	
Mrs. B.—								
Nonaerated	O	L	D	D	D	D	D	
Aerated 10 min.	O	F	L	L	L	L	L	
Mrs. G.—								
Nonaerated	O	O	O	F	L	L	L	
Aerated 15 min.	F	L	D	D	D	D	D	

TABLE III

11-19-22	2½ MIN.	5 MIN.	10 MIN.	15 MIN.	20 MIN.	30 MIN.	40 MIN.	1 HOUR
Mrs. H.—								
Nonaerated	O	O	O	F	F	L	L	
Aerated 10 min.	O	O	F	L	L	L	L	
15 min.	O	F	L	L	D	D	D	

a 500 watt Mazda lamp at a distance of 25 cm. Five-tenths c.c. of a 0.25 per cent solution of hydroquinon is then added. After this the color changes are noted at regular intervals. These changes range from a light yellow to a dark brown or black in some instances.

In this paper it is not our purpose to take up in any way the clinical interpretation of the Kottmann Reaction. Our observations have to do with the collection and handling of the specimen before the reaction is done and during its performance, and have both a practical and theoretical bearing. Soon after starting the tests we were able to easily verify an observation of previous

workers as to the marked variation in the reaction of a specimen of serum if preserved for any length of time, even though the interval be small and the serum be preserved in the ice box. Preservation has a tendency to accelerate the appearance of the color changes. Our policy has been to run tests as soon as possible after obtaining the specimens, and to keep our containers stoppered. Furthermore it was observed that after the addition of hydroquinon, the color change in the serums appeared around the top of the serums first, and was not uniform throughout the rest of the serum in each tube. In cases where retardation was slow there would often be a distinct ring of more pronounced darkening at the surface. This suggested the diminishing of the carbon dioxide content of the serum as a possible causative agent for this beginning change at the surface. This was based on the experience of one of us regarding the important relationship of carbon dioxide to photochemical reactions in the presence of albuminous substances. Abstraction of carbon dioxide causes a relatively important change in the acidity of the serum, and such a change is a fundamentally important variable in controlling the balance of chemical reactions, which is at the bottom of photochemical sensitivity. With this suggestion in mind the following experiments were carried out.

TABLE IV

11-20-22	2½ MIN.	5 MIN.	10 MIN.	15 MIN.	20 MIN.	30 MIN.	40 MIN.	1 HOUR
Mr. R.—								
Nonaerated	O	O	L	L	L	L		
Aerated 30 min.	D	D	D	D	D	D		
15 min.	D	D	D	D	D	D		
10 min.	F	L	L	D	D	D		
5 min.	F	L	L	D	D	D		
Nonaerated	O	O	L	L	L	L		

O—no change of color. F—faint brown color. L—light brown color. D—dark brown color.

Freshly drawn serum was obtained in all cases. The serum was then divided into several equal parts. Into one tube 1 c.c. of serum was placed and the tube stoppered—this specimen was not aerated. At the same time 1 c.c. quantities of the serum were placed in other similar tubes for aeration. Tubes to be aerated were clamped nearly horizontally, thus allowing the serum to present as large a surface as possible. Into each tube was inserted glass tubing extending nearly to the bottom of each tube, which in turn was connected to a suction pump, thus allowing a free suction of air across the exposed surface of the serum. Aeration of different serums in this manner at different lengths of time gave results of which the following are typical:

From these tables it will be noted that variations of the reaction can occur if aeration of the serum occurs in any way. Such might happen, for instance, by the simple exposure to air while the specimen is being centrifuged. A question immediately arises—Is this variation of reaction due to a loss of carbon dioxide, the most likely supposition, or could it be due to oxidation or exposure to light or some other unknown mechanism? To further decide as to the causative agent, the following experiment was performed:

A sample of freshly drawn serum was divided into unequal portions. The smaller (1 c.c.) portion was preserved in a stoppered tube for a few minutes until the larger portion could be thoroughly aerated in a rotated separatory funnel. After five minutes of such aeration 1 c.c. of serum was withdrawn for test and the atmosphere within the funnel was replaced by alveolar air from the operator's lungs. This was once renewed after the funnel had been rotated two and one-half minutes. The serum, in this manner, was again brought into approximately the same carbon dioxide equilibrium in which it had been within the body. The three specimens thus obtained were then simultaneously tested in the usual manner. Table V gives the results of this test:

TABLE V

Miss L.—	2½ MIN.	5 MIN.	10 MIN.	15 MIN.	20 MIN.	30 MIN.	1 HOUR	3 HOURS
Nonaerated	O	O	O	O	O	O	O	F
Aerated 5 min.	F	F	L	L	L	L	D	D
Resaturated	O	O	O	O	O	O	O	O

O—no change. F—faint brown. L—light brown. D—dark brown.

Note:—At the end of twenty-four hours complete reduction had taken place in the nonaerated and aerated specimens, but the resaturated one showed only partial reduction.

Certainly from these experiments it appears that the carbon dioxide content of the serum is playing a very important rôle in our readings of the Kottmann Reaction. Considering the fact that in most instances, decrease in the carbon dioxide content in the serum produces acceleration of color change and in other cases retardation results, it is probable that a still more fundamental variable, possibly hydrogen-ion concentration, is concerned. It should be noted also, that inasmuch as this particular source of error which we have found, has not heretofore been taken account of and as it affects in our experiments, the results in all cases; that all previous work with the Kottmann Reaction must be revised, fundamentally, from this standpoint. So important are small changes in the carbon dioxide content of the serum, that we must exercise great care in the application of the tourniquet, shortening as much as possible the duration of time in which it is applied before obtaining the specimen, thus avoiding any overaccumulation of carbon dioxide in the venous blood. In the future one of two methods will have to be followed—we will have to collect our blood samples under oil with all other precautions customarily employed in obtaining samples for the estimation of carbon dioxide content of blood plasma; or we must devise some method whereby the carbon dioxide error can be eliminated by a standard aeration of all blood serums.

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A SIMPLE METHOD FOR OBTAINING GUINEA PIGS' BLOOD FOR COMPLEMENT*

By B. S. Levine, Ph.D., Waukesha, Wis.

Director of the Clinical Laboratory, U. S. V. Hospital No. 37, (N. P.) Waukesha, Wisconsin.

IN obtaining blood from guinea pigs for complement used in the Wassermann reaction, it is desirable to avoid the use of anesthetics, since it is maintained by many serologists that anesthetics impair the complement quality of the blood serum. It is likewise desirable to reduce or, if possible, to

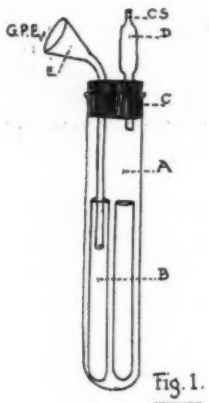

Fig. 1.

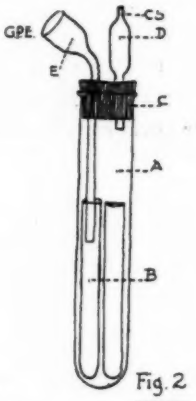

Fig. 2

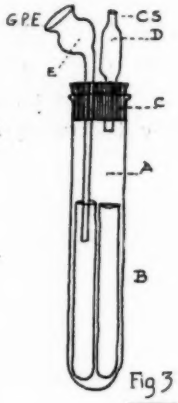

Fig 3

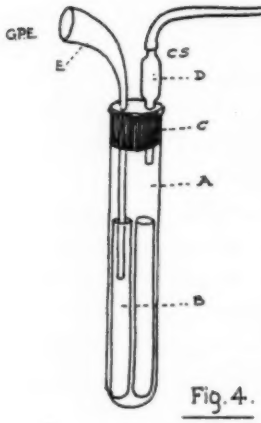

Fig. 4.

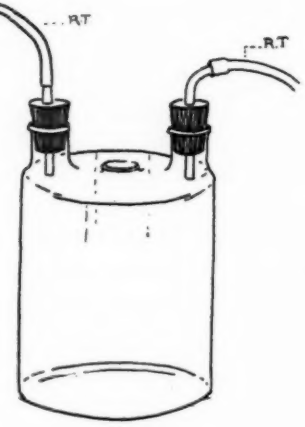

Fig. 5

eliminate entirely the mortality of the animals, caused by improper puncture or by excessive use of the anesthetic. This becomes especially desirable when one finds animals whose blood possesses a high complement titre.

Drawing blood from laboratory animals is frequently assigned to tech-

*Received for publication, March 5, 1923.

nical assistants whose operating skill is not always the best. Hence, the necessity for a method possessing the elements of simplicity, reliability, and safety arises. A method based on the principle of suction fulfills all these requirements, and is now in use in our laboratory with success.

Figs. 1, 2, 3, 4, 5 and 6 are schematic representations of the possible arrangements that can be used and in their simplicity are self-explanatory. The parts which are described below are obtainable in every diagnostic laboratory, and the combination can be set up in fifteen to thirty minutes.

(A) is a large heavy-walled pyrex glass tube.
(B) are Wassermann tubes into which the blood is collected.
(C) is a two-hole rubber stopper.
(D) is a connecting tube of glass.
(E) in Fig. 1 is made of a small-sized funnel.
— in Fig. 2 is made of a part of a 75 c.c. chemical pipette.
— in Fig. 3 is made of a thistle tube.
— in Fig. 4 is made of a drawn out heavy-walled medium-sized pyrex glass tube, and if bent as shown in the Figure is the best for the purpose.

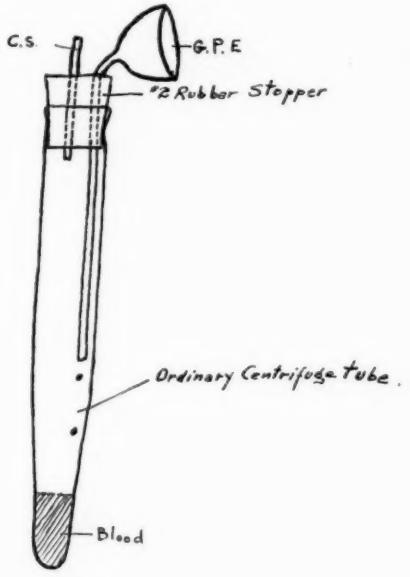

Fig. 6.

In obtaining the blood, suction is applied to the end marked C.S. through the Woulff flask, as is shown in the combination of Figs. 4 and 5. The ear of the animal is then washed, a small incision made, and the end of the glass arrangement marked G.P.E. is placed tightly over it. As soon as the skin of the animal seals the opening and a sufficient vacuum is created, the blood begins to flow from the incision into tube B. When a sufficient quantity of blood is drawn from one animal, another, or a third, and a fourth may be used. Two or three Wassermann tubes may be placed inside the large tube

A when a large quantity of serum is required. If some of the clotted blood collects at the end marked G.P.E., it is only necessary to push it with a clean glass rod into the neck wherefrom it will be carried down into the tube B by the suction. Figure 6 shows a still further simplified arrangement, that can be used with even greater ease than any of the above described. The drawing is self-explanatory.

This method of obtaining blood from the guinea pig requires no skill, and can be used successfully even by a beginner. It is safe, for the use of anesthetics and the necessity to "puncture in the dark" are completely eliminated.

Acknowledgment is here made to Dr. Grill of the Marquette Medical School, Department of Pathology and Bacteriology.

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EDITORIALS

*Life and Problems Under a Medical Utopia**

UNDER the above title, Carr in satire, has portrayed what we are coming to when the world is controlled by the doctors. All, of both sexes, on reaching the marriageable age will undergo strict and thorough medical examination. This will include not only the life-history of the individual but his or her ancestry so far as it can be traced. Ultimately, it will come about that every one will have a full pedigree from the time of the establishment of the Utopia. Those who are found fit will be given certificates, licensing them to marry, or at least to propagate their kind. Whether legal marriage will be required in Utopia is a matter left somewhat indefinite. All who cannot pass the examination will be sterilized so that they cannot beget children either in or outside of matrimony. The young couple, having passed these preliminary medical ordeals, will enter the marriage state. As soon as the wife becomes pregnant she will notify the proper authorities and she will be compelled to submit to an examination as frequently as the

*London Lancet, May 19, 1923.

medical officer may determine. The expectant mother will be relieved of all burdens in the way of work for a certain period before confinement. When the day set by the medical officer for confinement arrives the woman will go to a lying-in hospital. Artificial labor will be induced under proper aseptic precautions. The birth of the child will be duly registered and the mother before she leaves the hospital will be instructed in all particulars concerning breast-feeding. She will be required to take the infant every week to the hospital or dispensary in order that it may be weighed, its progress carefully watched, and its feeding superintended. When the child reaches the school age, all these procedures will be turned over to the school authorities. After her first confinement the mother will be carefully examined and notified whether or not she will be permitted to bear another child. How succeeding pregnancies are to be avoided is left somewhat uncertain. The couple may be advised to practice absolute and continuous continence. The author says that some advise this, but they are usually elderly folk who have forgotten that they ever had sex instincts or worthy ladies who perhaps never developed them or ecclesiastically minded celibates who are apparently anxious to make vicarious atonement for their own infertility by encouraging the highest possible fecundity in others. As a substitute for absolute continence various mechanical preventives or contraceptives may be furnished the married couple.

When the child reaches a certain age it will be carried to the surgeon, and if a boy will be circumcised, while in both sexes the appendix will be removed. The author is quite certain that at some specific age the entire large intestine will be removed from all. He justifies this procedure by high authority. He cites Metchnikoff, who wrote: "It is no longer rash to say that not only the rudimentary appendix and the cecum but the whole of the large intestine are superfluous and that their removal would be attended with happy results." Dr. Barclay Smith writes: "The statement is perhaps a bold one, but I am convinced that the large intestine is a practically useless incumbrance to man." Every year this opinion apparently grows and recently Sir Arbuthnot Lane informs us that he has performed, with complete success, colectomy in early childhood. "Since it has been discovered that the large intestine is a cesspool, certainly everybody should get rid of the cesspool which he carries around with him, as well as that which he formerly built in his back yard."

The next thing is to attend to the teeth. Since recent experiences have shown that pyorrhea is a constant menace to the health and a frequent cause of ill health, all the teeth of the second set should be drawn soon after their appearance and artificial ivories substituted. Of course, every child some time early in life will be not only vaccinated, but treated with a multivalent extract of all the organs in the body. The eyesight will be looked after and spectacles will be in great demand. The most serious thing, however, will be to follow the advice of Freud and practice psychotherapy upon all. Carr says, how marvelous, for instance, to discover, owing to a patient getting blocked on the simple word "long" that all her troubles were due to

her "longing" for a certain young man, whose offer of marriage she had rejected in haste, afterwards repenting at leisure of her refusal! How instructive to read that a young man who has been stammering for several years is easily and perfectly cured when it is realized that his difficulty in articulation was worse for words commencing with "K" and that this was the first letter of the name of a former sweetheart who had jilted him in favor of another man! Indeed, in Utopia the demand for psychotherapy will be unlimited.

Carr's description of how venereal diseases are to be handled is exceedingly interesting. Freudian teaching indicates that if we suppress our sexual desires we are going to suffer from this action sooner or later. It is highly desirable, therefore, that all sexual enticements should be gratified. Every young man will be required to carry with him constantly a prophylactic packet. It is true that he will be advised to practice continence, but it will be recognized that the sexual appetite is strong and that any young man may meet with temptations which he cannot resist, or at least he will not.

After giving us several pages of interesting satire the author drops into common sense and writes: "Probably the greatest danger under a medical autocracy would be that of loss of freedom. A distinguished ecclesiastic once caused quite a grave scandal by saying that he would rather see England free than England sober. I think he was right, and I believe it would be equally correct to say that we would rather see England free than England perfectly healthy. A despotism may be theoretically the best form of government if the ideal despot can be found, but he never can be, for human nature is so constituted that the mere fact of entrusting absolute power to an individual or a group of individuals soon renders them unfit to exercise that power over their fellow creatures. A medical despotism would be no exception to the rule. It is no sufficient answer to say that medical government would be necessarily in the best interests of the governed. A man's conception of what is best for his fellows may be absolutely disinterested and honest, his intentions may be wise and unselfish, but his conclusions and decisions may be erroneous, although the more convinced he is that he is doing right and that he is actuated by the highest and noblest principles, the more likely is he to become a tyrant. The exercise of uncontrolled power is almost always a cause of demoralization, and conscientiousness has to account for some of the darkest chapters of human history."

We have no fear that medical despotism, as portrayed in satire by Carr, will ever prevail on earth. Even if invested with absolute autocracy the medical profession is too sensible to lead the world so far astray.

—*V. C. V.*

A Transfer to Younger Shoulders

VOLUME VIII of this Journal will soon reach its close. With the September number I am turning over the editorship to Dr. Warren T. Vaughan, Professional Building, Richmond, Virginia. I am herewith asking that after the publication of this notice contributors direct all communications to the above address.

The Journal has acquired a worthy standing, and I do not think I am overstating the matter when I say that it has become the standard publication for laboratory methods and laboratory research along medical lines in this country. However, the Journal speaks for itself and I am willing that my labors as editor-in-chief shall be judged by their fruits. I have reached the period in life when I wish to retire, in part at least, from work. It gives me great pleasure to testify to the cordial relations that have existed and continue to exist between myself and my associate editors, my contributors, and the publishers. The last-mentioned have done everything in their power to make the publication creditable alike to themselves, their contributors, and the profession. My best wishes are for continued success, and I hope from time to time to be able to contribute to the Journal.

—*V. C. V.*

BOOK REVIEWS

(Books for Review should be sent to Dr. Warren T. Vaughan, 404 Professional Building, Richmond, Va.)

*Jordan's Bacteriology**

ORIGINALLY the outgrowth of lectures given to students in the University of Chicago, this book has developed into a textbook of bacteriology standard throughout the country. The general arrangement of the book is not changed from that of previous editions. The chapters on Influenza and Anaërobes have been entirely rewritten and the chapters on Streptococci, Pneumococci and Typhus Fever extensively revised. Additions have been made under the subjects of Immunity, Yellow Fever, etc. The chapter on the methods of study of bacteria has been rewritten and considerably enlarged. The author feels that we must provisionally accept leptospira icteroides as the cause of yellow fever. Concerning influenza, he remarks that the most promising work is that of Olitsky and Gates. Under the anaërobes, he discusses the newer work on botulism.

The author adopts the recent classification of the meningococcus, micrococcus catarrhalis and gonococcus, under the genus "Neisseria."

*General Bacteriology. A textbook by Edwin O. Jordan, Ph.D., Professor of Bacteriology in the University of Chicago and in the Rush Medical College. Seventh edition. Thoroughly revised. Cloth. Price $5.00. Pp. 744. Fully illustrated. Philadelphia and London. W. B. Saunders Company, 1922.